

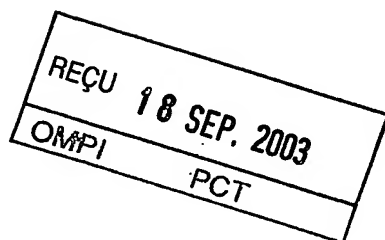


Rec'd PCT/PTO 14 FEB 2005
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INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ



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Signed

Stephen Hordley

Dated 23 July 2003

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The
Patent
Office

1/77

25APR03 E802446-1 D01030
P01/7700 0.00-0309326.7

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference

SCH/JW/P33099P1

2. Patent application number

(The Patent Office will fill in his part)

24 APR 2003

0309326.7

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Patents ADP number (if you know it)

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

473587003

4. Title of the invention

Compounds

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

Patents ADP number (if you know it)

Corporate Intellectual Property

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

76782003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and (if you know it) the or each application number

Country Priority application number Date of filing
(if you know it) (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer yes if:

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is named as an applicant, or
 - c) any named applicant is a corporate body
- See note (d)

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form.
Do not count copies of the same document

Continuation sheets of this form
Description
Claim(s)
Abstract
Drawings

113
2
1



10. If you are also filing any of the following,
state how many against each item.

Priority Documents

Translations of priority documents

Statement of inventorship and right
to grant of a patent (*Patents Form 7/77*)

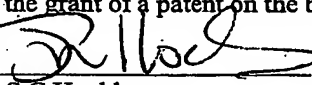
Request for preliminary examination
and search (*Patents Form 9/77*)

Request for substantive examination
(*Patents Form 10/77*)

Any other documents
(*please specify*)

11.

We request the grant of a patent on the basis of this
application

Signature  Date 24-Apr-03
S C Hockley

12. Name and daytime telephone number of
person to contact in the United Kingdom

S C Hockley 01279 644355

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Notes

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- b) Write your answers in capital letters using black ink or you may type them.
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- d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.
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Compounds

The present invention relates to novel pyrimidine derivatives, pharmaceutical compositions containing these compounds and their use in the treatment of diseases, particularly pain, which diseases are caused directly or indirectly by an increase or decrease in activity of the cannabinoid receptor.

Cannabinoids are a specific class of psychoactive compounds present in Indian cannabis (*Cannabis sativa*), including about sixty different molecules, the most representative being cannabitol, cannabidiol and several isomers of tetrahydrocannabinol. Knowledge of the therapeutic activity of cannabis dates back to the ancient dynasties of China, where, 5,000 years ago, cannabis was used for the treatment of asthma, migraine and some gynaecological disorders. These uses later became so established that, around 1850, cannabis extracts were included in the US Pharmacopoeia and remained there until 1947.

Cannabinoids are known to cause different effects on various systems and/or organs, the most important being on the central nervous system and on the cardiovascular system. These effects include alterations in memory and cognition, euphoria, and sedation. Cannabinoids also increase heart rate and vary systemic arterial pressure. Peripheral effects related to bronchial constriction, immunomodulation, and inflammation have also been observed. The capability of cannabinoids to reduce intraocular pressure and to affect respiratory and endocrine systems is also well documented. See e.g. L.E. Hollister, *Health Aspects of Cannabis*, Pharmacological Reviews, Vol. 38, pp. 1-20, (1986). More recently, it was found that cannabinoids suppress the cellular and humoral immune responses and exhibit anti-inflammatory properties. Wirth et al., *Anti-inflammatory Properties of Cannabichrome*, Life Science, Vol. 26, pp. 1991-1995, (1980).

In spite of the foregoing benefits, the therapeutic use of cannabis is controversial, both due to its relevant psychoactive effects (causing dependence and addiction), and due to manifold side effects that have not yet been completely clarified. Although work in this field has been ongoing since the 1940's, evidence indicating that the peripheral effects of cannabinoids are directly mediated, and not secondary to a CNS effect, has been limited by the lack of receptor characterisation, the lack of information concerning an endogenous cannabinoid ligand and, until recently, the lack of receptor subtype selective compounds.

The first cannabinoid receptor was found to be mainly located in the brain, in neural cell lines, and, only to a lesser extent, at the peripheral level. In view of its location, it was called the central receptor ("CB1"). See Matsuda et al., "Structure of a Cannabinoid Receptor and Functional Expression of the Cloned cDNA," Nature, Vol. 346, pp. 561-564 (1990). The second cannabinoid receptor ("CB2") was identified in the spleen, and was assumed to modulate the non psychoactive effects of the cannabinoids. See Munro et al., "Molecular Characterization of a Peripheral Receptor for Cannabinoids," Nature, Vol. 365, pp. 61-65 (1993).

Recently, some compounds have been prepared which are capable of acting as agonists on both the cannabinoid receptors. For example, use of derivatives of dihydroxypyrrole-(1,2,3-d,e)-1,4-benzoxazine in the treatment of glaucoma and the use of derivatives of 1,5-diphenylpyrazole as immunomodulators or psychotropic agents in the treatment of various neuropathologies, migraine, epilepsy, glaucoma, etc are known. See U.S. Patent No. 5,112,820

and EP 576357, respectively. However, because these compounds are active on both the CB1 and CB2 receptor, they can lead to serious psychoactive effects.

The foregoing indications and the preferential localisation of the CB2 receptor in the immune system confirms a specific role of CB2 in modulating the immune and anti-inflammatory response to stimuli of different sources.

The total size of the patient population suffering from pain is vast (almost 300 million), dominated by those suffering from back pain, osteo-arthritic pain and post-operative pain. Neuropathic pain (associated with neuronal lesions such as those induced by diabetes, HIV, herpes infection, or stroke) occurs with lower, but still substantial prevalence, as does cancer pain.

The pathogenic mechanisms that give rise to pain symptoms can be grouped into two main categories:

- those that are components of inflammatory tissue responses (Inflammatory Pain);
- those that result from a neuronal lesion of some form (Neuropathic Pain).

Chronic inflammatory pain consists predominantly of osteo-arthritis, chronic low back pain and rheumatoid arthritis. The pain results from acute and on-going injury and/or inflammation. There may be both spontaneous and provoked pain.

There is an underlying pathological hypersensitivity as a result of physiological hyperexcitability and the release of inflammatory mediators which further potentiate this hyperexcitability. CB2 receptors are expressed on inflammatory cells (T cells, B cells, macrophages, mast cells) and mediate immune suppression through inhibition of cellular interaction/ inflammatory mediator release. CB2 receptors may also be expressed on sensory nerve terminals and therefore directly inhibit hyperalgesia.

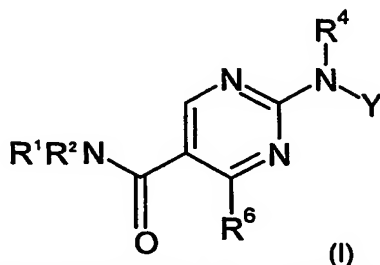
The role of CB2 in immunomodulation, inflammation, osteoporosis, cardiovascular, renal and other disease conditions is now being examined. In light of the fact that cannabinoids act on receptors capable of modulating different functional effects, and in view of the low homology between CB2 and CB1, the importance of developing a class of drugs selective for the specific receptor sub-type is evident. The natural or synthetic cannabinoids currently available do not fulfil this function because they are active on both receptors.

Based on the foregoing, there is a need for compounds which are capable of selectively modulating the receptor for cannabinoids and, therefore, the pathologies associated with such receptors. Thus, CB2 modulators offer a unique approach toward the pharmacotherapy of immune disorders, inflammation, osteoporosis, renal ischemia and other pathophysiological conditions.

The present invention provides novel pyrimidine derivatives of formula (I) and pharmaceutically acceptable derivatives thereof, pharmaceutical compositions containing these compounds or derivatives, and their use as CB2 receptor modulators, which are useful in the treatment of a variety of disorders.

The present invention further comprises a method for treating disease mediated by CB2 receptors in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

The invention provides compounds of formula (I):



wherein:

Y is phenyl, optionally substituted with one, two or three substituents;

R¹ is selected from: hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or halosubstituted C₁₋₆ alkyl;

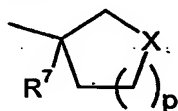
R² is (CH₂)_mR³ where m is 0 or 1;

or R¹ and R² together with N to which they are attached form an optionally substituted 4- to 8- membered non-aromatic heterocyclyl ring;

R³ is an optionally substituted 4- to 8- membered non-aromatic heterocyclyl group, an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted straight or branched C₁₋₁₀ alkyl, a C₅₋₇ cycloalkenyl or R⁵;

R⁴ is selected from: hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or halosubstituted C₁₋₆ alkyl, COCH₃, or SO₂Me;

R⁵ is



wherein p is 0, 1 or 2 and X is CH₂ or O;

R⁶ is methyl, chloro or CHXFn wherein n is 1, 2, or 3, x is 0, 1 or 2 and n and x add up to 3;

R⁷ is OH, C₁₋₆alkoxy, NR^{8a}R^{8b}, NHCOR⁹, NHSO₂R⁹, SOqR⁹;

R^{8a} is H or C₁₋₆alkyl;

R^{8b} is H or C₁₋₆alkyl;

R⁹ is C₁₋₆alkyl;

q is 0, 1 or 2;

and pharmaceutically acceptable derivatives thereof.

Preferably Y is a substituted phenyl. Preferably Y is substituted by 1, or 2 substituents.

If mono-substituted preferably the substituent is in the 3 position. If di-substituted preferably the substituents are in the 2,4- positions.

When Y is substituted, the substituent or substituents are preferably selected from: C₁₋₆ alkyl, halosubstituted C₁₋₆ alkyl, C₁₋₆ alkoxy, a hydroxy group, a cyano group, halo, a C₁₋₆alkyl sulfonyl group, -CONH₂, -NHCOCH₃ or -COOH. Furthermore the substituent or substituents can be selected from halosubstituted C₁₋₆ alkoxy, SO₂NR^{8a}R^{8b} wherein R^{8a} and R^{8b} are as defined above.

Preferably Y is substituted by halo, cyano or methoxy.

Preferably R¹ is hydrogen.

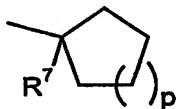
Preferably R^4 is C_{1-6} alkyl or hydrogen, more preferably methyl or hydrogen even more preferably hydrogen.

Alternatively R^1 and R^2 together with N to which they are attached form an optionally substituted 5- or 6- membered non-aromatic heterocyclyl ring.

5 When R^1 and R^2 together with N to which they are attached form a 5- or 7- membered non-aromatic heterocyclyl ring which is substituted, or when R^3 is substituted, the substituent or substituents are preferably selected from: C_{1-6} alkyl, C_{1-6} alkoxy, a hydroxy group, a cyano group, halo or a sulfonyl group. Additionally the optional substituent(s) can be chosen from methylsulfonyl, $NR^{8a}R^{8b}$, $NHCOCH_3$, $(=O)$, or $-CONHCH_3$.

10 Preferably R^6 is $CHxF_n$, for example CF_3 , CHF_2 , CH_2F , more preferably CF_3 .

Preferably R^5 is



wherein p is 0, 1 or 2;

Preferably R^7 is OH.

15 Preferably R^3 is an optionally substituted 4- to 8- membered non-aromatic heterocyclyl group, an optionally substituted C_{3-8} cycloalkyl group, an optionally substituted straight or branched C_{1-10} alkyl or R^5 .

Preferably when R^3 is an optionally substituted C_{3-8} cycloalkyl group or an optionally substituted 4- to 8- membered nonaromatic heterocyclyl, m is 1.

20 Preferably, R^3 is an optionally substituted C_{3-6} cycloalkyl group or an optionally substituted 4- or 6- membered nonaromatic heterocyclyl.

Preferably the compounds are selective for CB2 over CB1. Preferably the compounds are 100 fold selective or have less than 10% efficacy at the CB1 receptor.

The invention is described using the following definitions unless otherwise indicated.

25 The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of such ester or solvate of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

30 It will be appreciated by those skilled in the art that compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds, and that the compounds of formula (I) may be derivatised at more than one position.

35 It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically acceptable salts, but other salts may find use, for example in the preparation of compounds of formula (I) and the physiological acceptable salts thereof. Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, J. Pharm. Sci., 1977, 66, 1-19. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines

including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropyl amine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like.

Preferred examples of pharmaceutically acceptable salts include the ammonium, calcium, magnesium, potassium, and sodium salts, and those formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, hydrochloric, sulfuric, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, cyclohexylsulfamic, phosphoric and nitric acids.

The terms 'halogen or halo' are used to represent fluorine, chlorine, bromine or iodine.

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group or combinations thereof, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, pentyl, hexyl, 1,1-dimethylethyl, or combinations thereof.

The term 'alkoxy' as a group or as part of a group means a straight, branched or cyclic chain alkyl group having an oxygen atom attached to the chain, for example a methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy group, pentoxy, hexyloxy group, cyclopentoxy or cyclohexyloxy group.

The term 'cycloalkyl' means a closed non-aromatic ring, for example cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, or cyclooctyl.

The term 'cycloalkenyl' as a group or part of a group means a non-aromatic ring, containing at least one CH=CH moiety for example cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl, or cyclooctenyl.

When R¹ and R² taken together with the N to which they are attached form an optionally substituted heterocyclcyl ring, the ring may optionally contain 1, 2, 3 or 4 further heteroatoms. The ring may be saturated or unsaturated. Preferably the further heteroatoms are selected from oxygen, nitrogen or sulphur. An example of a 4- membered heterocyclcyl ring is azetidiny. Examples of 5- membered heterocyclcyl rings include pyrrolidinyl. Examples of 6-membered heterocyclcyl rings are morpholinyl, piperizinyl or piperidinyl. An additional example is tetrahydropyridinyl. Examples of a 7- membered heterocyclcyl ring are azapine or oxapine. Examples of 8-membered heterocyclcyl rings are azacyclooctanyl, azaoxacyclooctanyl or azathiacyclooctanyl.

When R³ is an optionally substituted non-aromatic heterocyclcyl group, the ring may contain 1, 2, 3, or 4 heteroatoms. Preferably the heteroatoms are selected from oxygen, nitrogen or sulphur. Examples of 4- membered groups are 2- or 3- azetidiny, oxetanyl, thioxetanyl, thioxetanyl-s-oxide, thioxetanyl-s,s-dioxide. Examples of 5- membered heterocyclcyl groups in this instance include dioxalanyl, pyrrolidinyl or tetrahydrofuranyl or tetrahydrothiophenyl.

Examples of 6-membered heterocyclyl groups are morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, thiomorpholinyl or thiomorpholinyl-s,s-dioxide. An additional example is tetrahydropyridinyl. Examples of a 7-membered heterocyclyl ring are azapine or oxapine. Examples of 8-membered groups are azacyclooctanyl, azaoxacyclooctanyl or azathiacyclooctanyl, oxacyclooctanyl, or thiacyclooctanyl.

Preferred compounds of the present invention can be selected from:

- 1-[2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-piperidin-1-ylmethanone;
- 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid
cyclopentylmethylamide;
- 10 [2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone;
- 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-
(cyclohexylmethyl)amide;
- 2-Phenylamino-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclohexylmethyl)amide;
- [2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone;
- 15 [2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone;
- [2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone;
- [2-(2,5-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone;
- [2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone;
- [2-(3-Bromophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone;
- 20 [2-(3-Bromophenylamino)-4-trifluoromethylpyrimidin-5-yl]-piperidin-4-ylmethanone;
- [2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone;
- 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-carboxylic acid N-cyclopentylamide;
- 2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-
(cyclohexylmethyl)amide;
- 25 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-
(cyclohexylmethyl)amide;
- 2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-
(cyclohexylmethyl)amide;
- 2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-
(cyclohexylmethyl)amide
- 30 2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-
(cyclohexylmethyl)amide;
- 2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-
(cyclohexylmethyl)amide;
- 35 2-(2,6-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-
(cyclohexylmethyl)amide;
- 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydro-pyran-4-
ylmethyl)amide;
- 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-carboxylic acid N-cyclobutylamide;
- 40 2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydropyran-4-
ylmethyl)amide;
- 2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydropyran-4-
ylmethyl)amide;

- 2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydropyran-4-ylmethyl)amide;
- 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydropyran-4-ylmethyl)amide;
- 5 2-(2,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydropyran-4-ylmethyl)amide;
- 2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydropyran-4-ylmethyl)amide;
- 10 2-(3-Methoxyphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydropyran-4-ylmethyl)amide;
- 2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide;
- 2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide;
- 15 2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide;
- 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide;
- 2-(2,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide;
- 20 2-(2,6-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide;
- 2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide;
- 25 2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide;
- 2-(3-Methoxyphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide;
- 2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-cyclobutylamide;
- 30 2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-cyclobutylamide;
- 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-cyclobutylamide;
- 2-(2,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-cyclobutylamide;
- 2-(2,6-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-cyclobutylamide;
- 2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-cyclobutylamide;
- 35 2-(3-Methoxyphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-cyclobutylamide;
- 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclobutylmethyl)amide;
- 2-(2,6-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)amide;
- 40 2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide;
- 1-{2-[(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]}-1-(morpholin-4-yl)-methanone;

- 2-(3-Methoxyphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide;
- 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (1-hydroxycyclohexylmethyl)-amide;
- 5 2-(3-Bromophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (1-hydroxycyclohexylmethyl)-amide;
- 2-(3-Chloro-4-fluorophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide;
- 2-(3-Chloro-2-fluorophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide;
- 10 2-(5-Chloro-2-fluorophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide;
- 2-(4-Chloro-2-trifluoromethylphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide;
- 15 2-(3-Cyanophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide;
- 2-(3-Cyanophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide;
- 2-(3-Cyanophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclopentylmethyl-amide;
- 20 2-(4-Cyanophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide;
- 2-(4-Cyanophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)amide;
- 25 2-(4-Cyanophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclopentylmethyl-amide;
- 2-(3-Methoxy-5-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide;
- 2-(3,5-Bis(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide;
- 30 2-(3-Bromo-5-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide;
- 2-(3-Fluoro-5-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide;
- 35 2-(2-Fluoro-3-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide;
- 2-(2-Methylthio-3-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide;
- 2-(5-Chloro-2-methylphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclopentylmethyl)-amide;
- 40 2-(3-Chloro-4-methylphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide;

- 2-(3-Chloro-2-methylphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid
(tetrahydropyran-4-ylmethyl)-amide;
- 2-(4-Chloro-3-methoxyphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid
(tetrahydropyran-4-ylmethyl)-amide;
- 5 2-(4-Chloro-3-methylphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid
(tetrahydropyran-4-ylmethyl)-amide;
- 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-
methyl-amide;
- 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-methyl-
10 amide;
- 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-
methyl-amide;
- 2-(5-Chloro-2-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclobutylmethyl-amide;
- 15 2-(3,5-Difluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-
amide;
- 2-(3-Chloro-4-trifluoromethoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclobutylmethyl-amide;
- 2-(3-Chloro-4-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
20 cyclobutylmethyl-amide;
- 2-(3-Chloro-2-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclobutylmethyl-amide;
- 2-(3-Fluoro-4-trifluoromethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclobutylmethyl-amide;
- 25 2-(3-Chloro-4-cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclobutylmethyl-amide;
- 2-(3-Fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-
amide;
- 2-(3-Bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-
30 amide;
- 2-(2,3-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-
amide;
- 2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-
amide;
- 35 2-(2,5-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-
amide;
- 2-(2,6-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-
amide;
- 2-(3,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-
40 amide;
- 2-(3-Methoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-
amide;

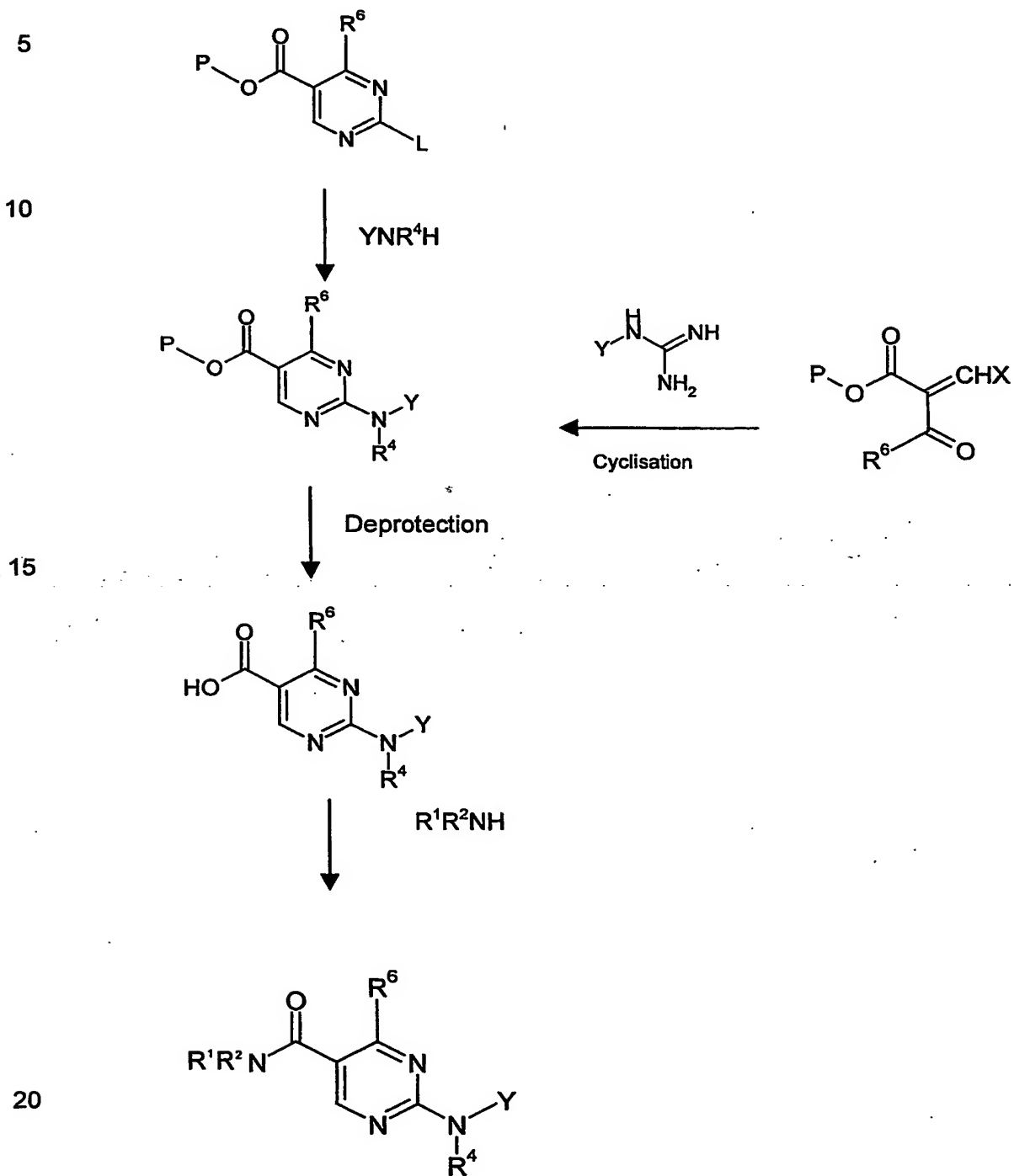
- 2-(3,5-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-
amide;
- 2-(3-Bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylamide;
- 2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid N-
- 5 cyclopentylamide;
- 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopropylamide;
- 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid N-(3,3-
dimethylbutyl)-amide;
- 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid methyl-(tetrahydro-
pyran-4-ylmethyl)-amide;
- 10 2-(2-Fluoro-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-
pyran-4-ylmethyl)-amide;
- 2-(2-Fluoro-5-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-
pyran-4-ylmethyl)-amide;
- 15 2-(3,5-Difluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-
4-ylmethyl)-amide;
- 2-(4-Fluoro-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-
pyran-4-ylmethyl)-amide;
- 2-(4-Trifluoromethoxy-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
(tetrahydro-pyran-4-ylmethyl)-amide;
- 20 2-(4-Cyano-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-
pyran-4-ylmethyl)-amide;
- 2-(4-Trifluoromethyl-3-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
(tetrahydro-pyran-4-ylmethyl)-amide;
- 25 2-(4-Cyano-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclopentylmethylamide;
- 2-(2,4-Dichloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (1,1-dioxo-
hexahydro-1⁶ - thiopyran-4-yl)-amide;
- 2-(2,4-Difluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-
amide;
- 30 2-(2-Chloro-4-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclohexylmethyl-amide;
- 2-(2,4-Difluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-
amide;
- 35 2-(2-Chloro-4-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclobutylmethyl-amide;
- 2-(2-Chloro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclohexylmethyl-amide;
- 2-(2-Fluoro-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclohexylmethyl-amide;
- 40 2-(2-Chloro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclobutylmethyl-amide;

- 2-(2-Fluoro-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclobutylmethyl-amide;
- 2-(2-Fluoro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclobutylmethyl-amide;
- 5 2-(2-Bromo-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclobutylmethyl-amide;
- 2-(2-Fluoro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclohexylmethyl-amide;
- 10 2-(2-Fluoro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-
pyran-4-ylmethyl)-amide;
- 2-(2-Chloro-4-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-
pyran-4-ylmethyl)-amide;
- 2-(2-Chloro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-
pyran-4-ylmethyl)-amide;
- 15 2-(2-Chloro-4-cyano-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-
pyran-4-ylmethyl)-amide;
- 2-(2-Chloro-4-trifluoromethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
(tetrahydro-pyran-4-ylmethyl)-amide;
- 2-(2-Chloro-4-cyano-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
20 cyclohexylmethyl-amide;
- 2-(2-Bromo-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclohexylmethyl-amide;
- 2-(2-Bromo-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-
pyran-4-ylmethyl)-amide;
- 25 2-(3-Bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopropylmethyl-
amide;
- 2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopropylmethyl-
amide;
- 2-(2,3-Difluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-
30 amide;
- 2-(2-Fluoro-3-trifluoromethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclohexylmethyl-amide;
- 2-(2-Chloro-4-methylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclohexylmethyl-amide;
- 35 2-(4-Chloro-3-methoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclohexylmethyl-amide;
- 2-(5-Chloro-2-methylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclohexylmethyl-amide;
- 2-(3-Chloro-4-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
40 cyclopentylmethyl-amide;
- 2-(3-Chloro-2-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclopentylmethyl-amide;

- 2-(2-Chloro-5-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclopentylmethyl-amide;
- 2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide;
- 5 2-(Phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethanamide;
2-(2-Fluoro-3-trifluoromethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclobutylmethyl-amide;
- 2-(2-Methyl-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
cyclobutylmethyl-amide;
- 10 2-(2-trifluoromethyl-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
(tetrahydro-pyran-4-ylmethyl)amide;
- 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydrothiopyran-4-ylmethyl) amide;
- 2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid
- 15 (tetrahydrothiopyran-4-ylmethyl) amide;
and pharmaceutically acceptable derivatives thereof.

Compounds of formula (I) can be prepared as set forth in the following schemes:

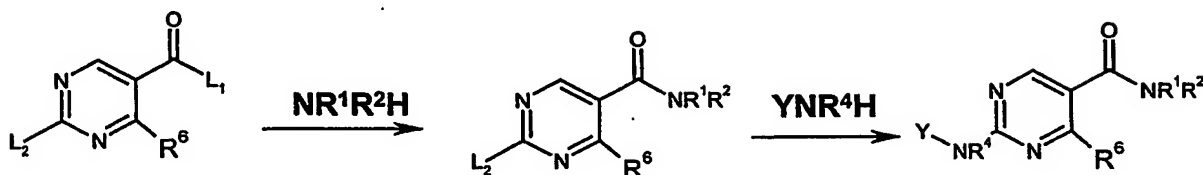
Scheme 1:



wherein L is a leaving group, for example halo, P is a protecting group for example methyl, ethyl or benzyl, X is a leaving group for example halo, OC₁₋₆alkyl, e.g. O-methyl or O-ethyl or NR^aR^b

wherein R^a and R^b are independently selected from C_{1-6} alkyl, e.g. methyl, and R^1 , R^2 , R^4 , R^6 and Y are as defined for compounds of formula (I).

Scheme 2:



wherein L_1 and L_2 are leaving groups independently selected from halo, for example chloro, R^1 , R^2 , R^4 , R^6 and Y are as defined for compounds of formula (I).

It is to be understood that the present invention encompasses all isomers of compounds of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates or solvates as well as compounds containing variable amounts of water and/or solvent.

The compounds of the invention bind selectively to the CB2 receptor, and are therefore useful in treating CB2 receptor mediated diseases.

In view of their ability to bind to the CB2 receptor, the compounds of the invention may be useful in the treatment of the disorders that follow. Thus, the compounds of formula (I) may be useful as analgesics. For example they may be useful in the treatment of chronic inflammatory pain (e.g. pain associated with rheumatoid arthritis, osteo-arthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease modification and joint structure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea.

The compounds of the invention may also be useful disease modification or joint structure preservation in multiple sclerosis, rheumatoid arthritis, osteo-arthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis.

The compounds of the invention may be particularly useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-

specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of formula (I) may also be useful in the treatment of fever.

The compounds of formula (I) may also be useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD)); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varioliforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, myaesthesia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Bèchet's syndrome, polymyositis, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, tendinitis, bursitis, and Sjogren's syndrome.

The compounds of formula (I) are also useful in the treatment of immunological diseases such as autoimmune diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) are also effective in increasing the latency of HIV infection.

The compounds of formula (I) are also useful in the treatment of diseases of abnormal platelet function (e.g. occlusive vascular diseases).

The compounds of formula (I) are also useful for the preparation of a drug with diuretic action.

The compounds of formula (I) are also useful in the treatment of impotence or erectile dysfunction.

The compounds of formula (I) are also useful for attenuating the hemodynamic side effects of non-steroidal anti-inflammatory drugs (NSAID's) and cyclooxygenase-2 (COX-2) inhibitors.

The compounds of formula (I) are also useful in the treatment of neurodegenerative diseases and neurodegeneration such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma;

infections and related conditions (including HIV infection); dementia in Parkinson's disease; metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment. The compounds may also be useful for the treatment of amyotrophic lateral sclerosis (ALS) and neuroinflammation.

5 The compounds of formula (I) are also useful in neuroprotection and in the treatment of neurodegeneration following stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

 The compounds of formula (I) are also useful in the treatment of tinnitus.

10 The compounds of formula (I) are also useful in the treatment of psychiatric disease for example schizophrenia, depression (which term is used herein to include bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder, dysthymic disorders with early or late onset and with or without atypical features, neurotic depression and social phobia, depression accompanying dementia for example
15 of the Alzheimer's type, schizoaffective disorder or the depressed type, and depressive disorders resulting from general medical conditions including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, *etc*), anxiety disorders (including generalised anxiety disorder and social anxiety disorder), panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder, memory disorders, including dementia, amnesic
20 disorders and age-associated memory impairment, disorders of eating behaviours, including anorexia nervosa and bulimia nervosa, sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy), withdrawal from abuse of drugs such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine (phencyclidine-like compounds), opiates (e.g. cannabis, heroin, morphine), amphetamine or
25 amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) or a combination thereof.

 The compounds of formula (I) are also useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent. Examples of dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g.
30 ethanol), psychostimulants (e.g. cocaine) and nicotine.

 The compounds of formula (I) are also useful in the treatment of kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), liver dysfunction (hepatitis, cirrhosis), gastrointestinal dysfunction (diarrhoea) and colon cancer.

35 It is to be understood that references to treatment includes both treatment of established symptoms and prophylactic treatment unless explicitly stated otherwise.

 According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

40 According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the activity of cannabinoid 2 receptors.

 According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the activity of cannabinoid 2

receptors which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from an immune disorder, an inflammatory disorder, pain, rheumatoid arthritis, multiple sclerosis, osteoarthritis or osteoporosis which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof. Preferably the pain is selected from inflammatory pain, visceral pain, cancer pain, neuropathic pain, lower back pain, muscular skeletal, post operative pain, acute pain and migraine. More preferably the inflammatory pain is pain associated with rheumatoid arthritis or osteoarthritis.

According to another aspect of the invention is provided the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment or prevention of a condition such as an immune disorder, an inflammatory disorder, pain, rheumatoid arthritis, multiple sclerosis, osteoarthritis or osteoporosis

Preferably the pain is selected from inflammatory pain, visceral pain, cancer pain, neuropathic pain, lower back pain, muscular skeletal, post operative pain, acute pain and migraine. More preferably the inflammatory pain is pain associated with rheumatoid arthritis or osteoarthritis.

In order to use a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. Therefore in another aspect of the invention is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.

As used herein, "modulator" means both antagonist, agonist and inverse agonist. Preferably the present modulators are agonists.

Compounds of formula (I) and their pharmaceutically acceptable derivatives may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, dermally, intranasally, transdermally, rectally, via inhalation or via buccal administration.

Compositions of formula (I) and their pharmaceutically acceptable derivatives which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or derivative in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

5 Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable derivative thereof which is active when administered in this way,
10 with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

15 Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.01mg/Kg to 500 mg/Kg, for example 0.1 mg to 500 mg/Kg, and preferably from 0.01 mg to 100 mg/Kg for example 1mg/Kg to 100mg/Kg, and each dosage unit for parenteral administration contains suitably from
20 0.1 mg to 100 mg/Kg, of a compound of formula (I) or a pharmaceutically acceptable derivative thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 5.0% of a compound of formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40
25 mg/Kg, of a compound of formula (I) or a pharmaceutically acceptable derivative thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of formula (I) or a pharmaceutically acceptable derivative thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active
30 ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

The CB₂ receptor compounds for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib or COX-189; 5-lipoxygenase inhibitors; NSAID's, such as aspirin, diclofenac, indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists;
35 DMARD's such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA receptor modulators, such as glycine receptor antagonists; gabapentin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; 5HT₁ agonists, such as triptans, for example sumatriptan, naratriptan,
40 zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; EP₁ receptor ligands, EP₄ receptor ligands; EP₂ receptor ligands; EP₃ receptor ligands; EP₄ antagonists; EP₂ antagonists and EP₃ antagonists; bradykinin receptor ligands and vanilloid receptor ligand, antirheumatoid arthritis drugs, for example anti TNF drugs e.g. enbrel, remicade, anti-IL-1 drugs, or DMARDS e.g.

leflunamide. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

Additional COX-2 inhibitors are disclosed in US Patent Nos. 5,474,995 US5,633,272; US5,466,823, US6,310,099 and US6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484, WO 97/14691, WO99/12930, WO00/26216, WO00/52008, WO00/38311, WO01/58881 and WO02/18374.

The compound of the present invention may be administered in combination with other active substances such as 5HT3 antagonists, NK-1 antagonists, serotonin agonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants and/or dopaminergic antidepressants.

Suitable 5HT3 antagonists which may be used in combination of the compound of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compound of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

Suitable SSRIs which may be used in combination with the compound of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

Suitable SNRIs which may be used in combination with the compound of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptyline, chlomipramine and nortriptyline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

It will be appreciated that the compounds of any of the above combinations or compositions may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

Determination of cannabinoid CB1 Receptor Agonist Activity

The cannabinoid CB1 receptor agonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

Yeast (*Saccharomyces cerevisiae*) cells expressing the human cannabinoid CB1 receptor were generated by integration of an expression cassette into the *ura3* chromosomal locus of yeast strain MMY23. This cassette consisted of DNA sequence encoding the human CB1 receptor flanked by the yeast GPD promoter to the 5' end of CB1 and a yeast transcriptional terminator sequence to the 3' end of CB1. MMY23 expresses a yeast/mammalian chimeric G-protein alpha subunit in which the C-terminal 5 amino acids of Gpa1 are replaced with the C-terminal 5 amino acids of human G α i3 (as described in Brown et al. (2000), *Yeast* 16:11-22). Cells were grown at 30°C in liquid Synthetic Complete (SC) yeast media (Guthrie and Fink (1991), *Methods in Enzymology*, Vol. 194) lacking uracil, tryptophan, adenine and leucine to late logarithmic phase (approximately 6 OD₆₀₀/ml).

Agonists were prepared as 10 mM stocks in DMSO. EC₅₀ values (the concentration required to produce 50% maximal response) were estimated using dilutions of between 3- and 5-fold (BiomekFX, Beckman) into DMSO. Agonist solutions in DMSO (1% final assay volume) were transferred into black, clear bottom, microtitre plates from NUNC (96- or 384-well). Cells were suspended at a density of 0.2 OD₆₀₀/ml in SC media lacking histidine, uracil, tryptophan, adenine and leucine and supplemented with 10mM 3-aminotriazole, 0.1M sodium phosphate pH 7.0, and 20µM fluorescein di-β-D-glucopyranoside (FDGlu). This mixture (50ul per well for 384-well plates, 200ul per well for 96-well plates) was added to agonist in the assay plates (Multidrop 384, Labsystems). After incubation at 30°C for 24 hours, fluorescence resulting from degradation of FDGlu to fluorescein due to exoglucanase, an endogenous yeast enzyme produced during agonist-stimulated cell growth, was determined using a Spectrofluor microtitre plate reader (Tecan; excitation wavelength: 485nm; emission wavelength: 535nm). Fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter fit to generate a concentration effect value. Efficacy (E_{max}) was calculated from the equation

$$E_{\max} = \frac{\text{Max}_{[\text{compound X}]} - \text{Min}_{[\text{compound X}]}}{\text{Max}_{[\text{HU210}]} - \text{Min}_{[\text{HU210}]}} \times 100\%$$

where Max_[compound X] and Min_[compound X] are the fitted maximum and minimum respectively from the concentration effect curve for compound X, and Max_[HU210] and Min_[HU210] are the fitted maximum and minimum respectively from the concentration effect curve for (6aR,10aR)-3-(1,1'-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol (HU210; available from Tocris). Equieffective molar ratio (EMR) values were calculated from the equation

$$\text{EMR} = \text{EC}_{50} [\text{compound X}] / \text{EC}_{50} [\text{HU210}]$$

Where EC₅₀ [compound X] is the EC₅₀ of compound X and EC₅₀ [HU210] is the EC₅₀ of HU210.

Compounds of the Examples tested according to this method had EC₅₀ values >2000nM and/or efficacy values of <50% at the cloned human cannabinoid CB1 receptor.

Determination of cannabinoid CB2 Receptor Agonist Activity

The cannabinoid CB2 receptor agonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

Yeast (*Saccharomyces cerevisiae*) cells expressing the human cannabinoid CB2 receptor were generated by integration of an expression cassette into the *ura3* chromosomal locus of yeast strain MMY23. This cassette consisted of DNA sequence encoding the human CB2 receptor flanked by the yeast GPD promoter to the 5' end of CB2 and a yeast transcriptional terminator sequence to the 3' end of CB2. MMY23 expresses a yeast/mammalian chimeric G-protein alpha subunit in which the C-terminal 5 amino acids of Gpa1 are replaced with the C-terminal 5 amino acids of human G α i3 (as described in Brown et al. (2000), *Yeast* 16:11-22). Cells were grown at 30°C in liquid Synthetic Complete (SC) yeast media (Guthrie and Fink (1991), *Methods in Enzymology*, Vol. 194) lacking uracil, tryptophan, adenine and leucine to late logarithmic phase (approximately 6 OD₆₀₀/ml).

Agonists were prepared as 10 mM stocks in DMSO. EC₅₀ values (the concentration required to produce 50% maximal response) were estimated using dilutions of between 3- and 5-fold (BiomekFX, Beckman) into DMSO. Agonist solutions in DMSO (1% final assay volume) were transferred into black, clear bottom, microtitre plates from NUNC (96- or 384-well). Cells were suspended at a density of 0.2 OD₆₀₀/ml in SC media lacking histidine, uracil, tryptophan, adenine and leucine and supplemented with 10mM 3-aminotriazole, 0.1M sodium phosphate pH 7.0, and 20M fluorescein di- β -D-glucopyranoside (FDGlu). This mixture (50ul per well for 384-well plates, 200ul per well for 96-well plates) was added to agonist in the assay plates (Multidrop 384, Labsystems). After incubation at 30°C for 24 hours, fluorescence resulting from degradation of FDGlu to fluorescein due to exoglucanase, an endogenous yeast enzyme produced during agonist-stimulated cell growth, was determined using a Spectrofluor microtitre plate reader (Tecan; excitation wavelength: 485nm; emission wavelength: 535nm). Fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter fit to generate a concentration effect value. Efficacy (E_{max}) was calculated from the equation

$$E_{\max} = \frac{\text{Max}_{[\text{compound X}]} - \text{Min}_{[\text{compound X}]}}{\text{Max}_{[\text{HU210}]} - \text{Min}_{[\text{HU210}]}} \times 100\%$$

where Max_[compound X] and Min_[compound X] are the fitted maximum and minimum respectively from the concentration effect curve for compound X, and Max_[HU210] and Min_[HU210] are the fitted maximum and minimum respectively from the concentration effect curve for (6aR,10aR)-3-(1,1'-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol (HU210; available from Tocris). Equieffective molar ratio (EMR) values were calculated from the equation

$$\text{EMR} = \text{EC}_{50} [\text{compound X}] / \text{EC}_{50} [\text{HU210}]$$

Where EC₅₀ [compound X] is the EC₅₀ of compound X and EC₅₀ [HU210] is the EC₅₀ of HU210.

Compounds of Examples 1 to 23, 31 to 56, 68, 163 – 256 tested according to this method had EC₅₀ values 20 to 300 nM and efficacy values of >50% at the cloned human cannabinoid CB2 receptor.

Compounds of Examples 24 to 30 and 73-113, and 257-259 tested according to this method had EC₅₀ values 300 to 1000nM or efficacy values of > 50% at the cloned human cannabinoid CB2 receptor.

Compounds of Examples 57-67, 69-72, 114-162, and 260-263 tested according to this method had EC₅₀ values > 1000nM or efficacy values of <50% at the cloned human cannabinoid CB2 receptor.

The following examples are illustrative, but not limiting of the embodiments of the present invention.

All NMR experimental data was recorded at 400MHz.

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Conditions, Hardware, and Software used for Mass-directed Autopurification

Hardware

10 Waters 600 gradient pump, Waters 2700 Sample Manager, Waters Reagent Manager, Micromass ZMD mass spectrometer, Gilson 202 - fraction collector, Gilson Aspec - waste collector.

Software

Micromass Masslynx version 3.5

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Column

The column used is typically a Supelco ABZ+ column whose dimensions are 10mm internal diameter by 100mm in length. The stationary phase particle size is 5µm.

Solvents

A. Aqueous solvent = Water + 0.1% Formic Acid

20 B. Organic solvent = MeCN: Water 95:5 +0.05% Formic Acid

Make up solvent = MeOH: Water 80:20 +50mMol Ammonium Acetate

Needle rinse solvent = MeOH: Water: DMSO 80:10:10

Methods

25 Five methods are used depending on the analytical retention time of the compound of interest. They all have a flow rate of 20ml/min and a 15-minute runtime, which comprises of a 10-minute gradient followed by a 5-minute column flush and re-equilibration step.

Method 1 MDP 1.5-2.2 = 0-30%B

Method 2 MDP 2.0-2.8 = 5-30% B

30 Method 3 MDP 2.5-3.0 = 15-55%B

Method 4 MDP 2.8-4.0 = 30-80% B

Method 5 MDP 3.8-5.5 = 50-90% B

Reference Example 1: 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid benzylamide

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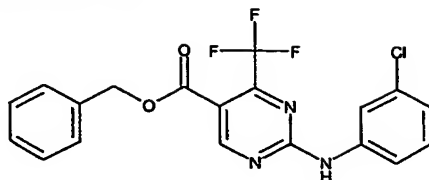
(a). To a solution of benzyl 2-chloro-4-trifluoromethylpyrimidine-5-carboxylate (0.50 g, ex Maybridge) in 1,4-dioxan (5 ml) was added 3-chloroaniline (0.85 ml) and the solution stirred at room temperature for 15 h. 1,4-Dioxan was removed under reduced pressure and ethyl acetate (15 ml) added. The solution was washed sequentially with 2N hydrochloric acid (10 ml) and water (3

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x 10 ml), dried (MgSO₄), evaporated and triturated with hexane to afford benzyl 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylate (524 mg).

NMR (DMSO-d₆) δ 5.35 (2H, s), 7.14 (1H, d), 7.35-7.45 (6H, m), 7.68 (1H, m), 7.98 (1H, s), 9.13 (1H, s), 10.95 (1H, s).

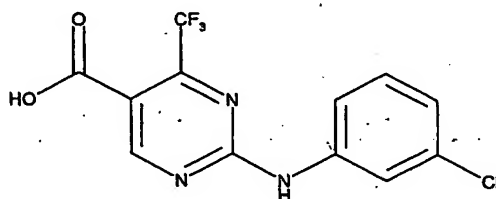
LC/MS, $t = 3.70$ min, $[MH^+]$ 408 and 410.



(b). To a solution of benzyl 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylate (0.50 g) in ethanol (15 ml) was added a solution of potassium hydroxide (205 mg) in ethanol (10 ml) and the solution stirred at reflux for 15 h. Ethanol was removed under reduced pressure and water (15 ml) added. The solution was washed with ether and concentrated hydrochloric acid added to adjust the acidity to pH 1. The precipitated solid was filtered, washed with water and dried in vacuo at 50°C to afford 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (366 mg).

NMR (DMSO- d_6) δ 7.49 (1H, d), 7.71 (1H, t), 7.98 (1H, d), 8.33 (1H, s), 9.42 (1H, s), 11.15 (1H, s), 14.0 (1H, br s).

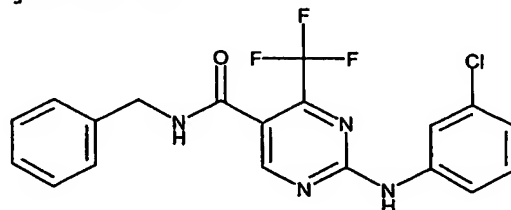
LC/MS, $t = 3.44$ min, $[MH^+]$ 318 and 320.



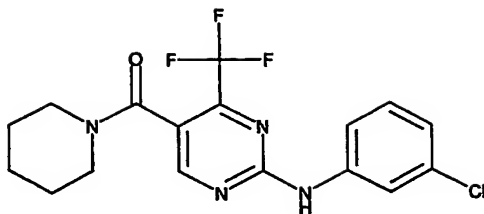
(c). To a solution of 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) in dimethylformamide (2 ml) was added successively N-ethylmorpholine (42 μ l), benzylamine (15 μ l), 1-hydroxybenzotriazole hydrate (23 mg) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (25 mg). The solution was stirred for 3 h and allowed to stand overnight. Dimethylformamide was removed under reduced pressure and ethyl acetate (5 ml) added. The solution was washed sequentially with 5% sodium bicarbonate solution (2.5 ml), water (2.5 ml), 5% citric acid solution (2.5 ml) and brine (2 x 2.5 ml), dried ($MgSO_4$) and evaporated to afford the title compound (45 mg).

NMR (DMSO- d_6) δ 4.47 (2H, d), 7.10 (1H, d), 7.25 (1H, m), 7.36 (5H, m), 7.69 (1H, d), 7.98 (1H, s), 8.89 (1H, s), 9.12 (1H, t), 10.65 (1H, s).

LC/MS, $t = 3.23$ min, $[MH^+]$ 407 and 409.



Example 1: 1-[2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]piperidin-1-ylmethanone



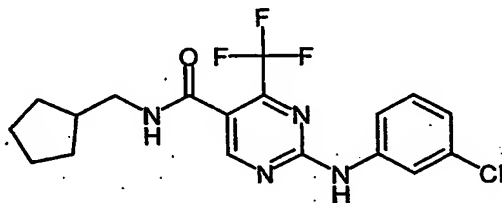
5 In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and piperidine (13 μ l) afforded the title compound (38 mg).

NMR (DMSO- d_6) δ 1.3-1.65 (6H, m), 3.28 (2H, s), 3.6 (2H, br s), 7.10 (1H, d), 7.37 (1H, t), 7.68 (1H, d), 7.96 (1H, s), 8.78 (1H, s), 10.55 (1H, s).

LC/MS, $t = 3.63$ min, $[MH^+]$ 385 and 387.

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Example 2: 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylmethylamide

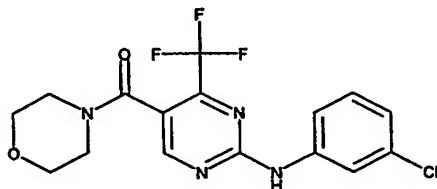


15 In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (100 mg) and cyclopentylmethylamine hydrochloride (63 mg, prepared as described in Kelley et al., J. Med. Chem., **40**, 3207, (1997)) afforded the title compound (80 mg).

NMR (DMSO- d_6) δ 1.20-1.26 (2H, m), 1.48-1.67 (4H, m), 1.67-1.73 (2H, m), 2.06-2.10 (1H, quintuplet), 3.15-3.18 (2H, t), 7.09 (1H, dt), 7.37 (1H, q), 7.67 (1H, d), 7.96 (1H, d), 8.60-8.63 (1H, t), 8.79 (1H, s), 10.60 (1H, s).

20 LC/MS, $t = 3.73$ min, $[MH^+]$ 399.

Example 3: [2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]morpholin-4-yl-methanone

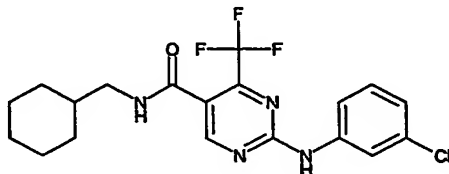


25 In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and morpholine (11.5 μ l) afforded the title compound (43 mg).

NMR (DMSO- d_6) δ 3.4-3.75 (8H, m), 7.10 (1H, d), 7.38 (1H, t), 7.68 (1H, d), 7.98 (1H, s), 8.80 (1H, s), 10.60 (1H, s).

30 LC/MS, $t = 3.29$ min, $[MH^+]$ 387 and 389.

Example 4: 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclohexylmethyl)amide

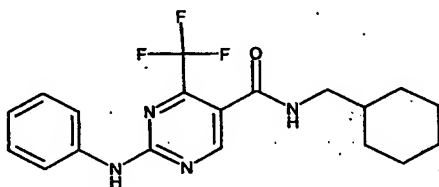


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In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and cyclohexanemethylamine (15 mg) afforded the title compound (27 mg).

10 NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.3 (3H, m), 1.5 (1H, m), 1.55-1.8 (5H, m), 3.06 (2H, t), 7.09 (1H, d), 7.37 (1H, t), 7.68 (1H, d), 7.97 (1H, s), 8.58 (1H, t), 8.79 (1H, s), 10.6 (1H, s).
LC/MS, $t = 3.87$ min, $[MH^+]$ 413 and 415.

Example 5: 2-Phenylamino-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclohexylmethyl)amide



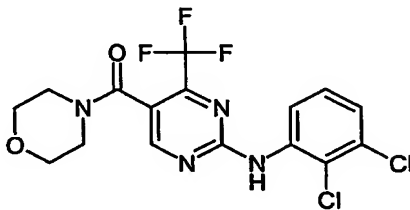
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In a manner similar to Reference Example 1(c) 2-phenylamino-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclohexanemethylamine (15 mg) afforded the title compound (33 mg).

20 NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.05-1.3 (3H, m), 1.5 (1H, m), 1.55-1.8 (5H, m), 3.08 (2H, t), 7.06 (1H, d), 7.35 (2H, t), 7.76 (2H, d), 8.56 (1H, t), 8.74 (1H, s), 10.4 (1H, s).
LC/MS, $t = 3.66$ min, $[MH^+]$ 379.

Example 6: [2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone

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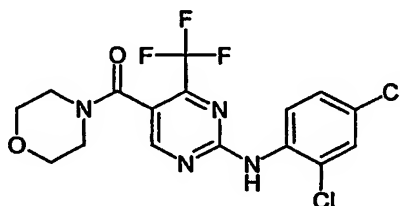
In a manner similar to Reference Example 1(c) 2-(2,3-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (24 mg) and morpholine (10 μ l) afforded the title compound (17 mg).

30 NMR (DMSO-d₆) δ 3.4-3.8 (8H, m), 7.40 (1H, t), 7.54 (1H, d), 7.60 (1H, d), 8.78 (1H, s), 10.15 (1H, s).

LC/MS, $t = 3.32$ min, $[MH^+]$ 421 and 423.

Example 7: [2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone

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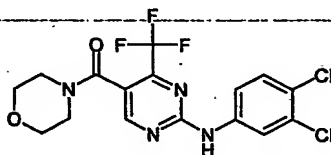
In a manner similar to Reference Example 1(c) 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (30 mg) and morpholine (10 μ l) afforded the title compound (31 mg).

10 NMR (DMSO- d_6) δ 3.3-3.8 (8H, m), 7.52 (1H, d of d), 7.68 (1H, d), 7.76 (1H, d), 8.73 (1H, s), 10.05 (1H, s).

LC/MS, $t = 3.37$ min, $[MH^+]$ 421 and 423.

Example 8: [2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone

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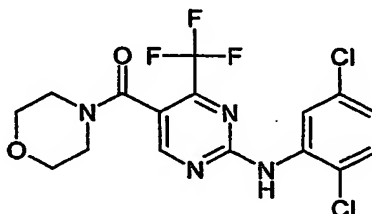
In a manner similar to Reference Example 1(c) 2-(3,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (30 mg) and morpholine (10 μ l) afforded the title compound (36 mg).

20 NMR (DMSO- d_6) δ 3.35-3.8 (8H, m), 7.67 (1H, d), 7.76 (1H, d of d), 8.22 (1H, s), 8.90 (1H, s), 10.80 (1H, s).

LC/MS, $t = 3.45$ min, $[MH^+]$ 421 and 423.

Example 9: [2-(2,5-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone

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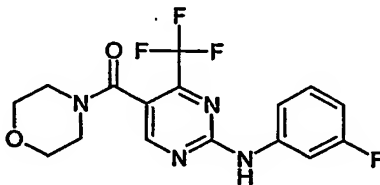
In a manner similar to Reference Example 1(c) 2-(2,5-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and morpholine (14.5 μ l) afforded the title compound (27 mg).

30 NMR (DMSO- d_6) δ 3.4-3.75 (8H, m), 7.32 (1H, d of d), 7.66 (1H, d), 7.78 (1H, d), 8.71 (1H, s), 10.05 (1H, s).

LC/MS, $t = 3.31$ min, $[MH^+]$ 421 and 423.

Example 10: [2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone

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In a manner similar to Reference Example 1(c) 2-(3-fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and morpholine (12 μ l) afforded the title compound (31 mg).

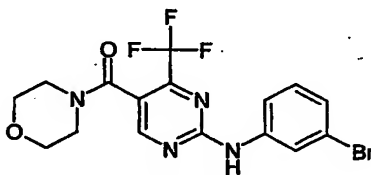
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NMR (DMSO- d_6) δ 3.4-3.8 (8H, m), 6.85 (1H, t of d), 7.37 (1H, q), 7.52 (1H, d), 7.77 (1H, d of t), 8.80 (1H, s), 10.65 (1H, s).

LC/MS, $t = 3.06$ min, $[MH^+]$ 371.

Example 11: [2-(3-Bromophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone

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In a manner similar to Reference Example 1(c) 2-(3-bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and morpholine (10 μ l) afforded the title compound (31 mg).

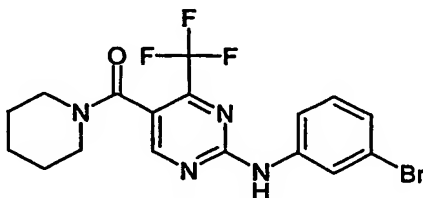
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NMR (DMSO- d_6) δ 3.4-3.8 (8H, m), 7.22 (1H, d), 7.30 (1H, t), 7.71 (1H, d), 8.11 (1H, s), 8.81 (1H, s), 10.60 (1H, s).

LC/MS, $t = 3.25$ min, $[MH^+]$ 431 and 433.

Example 12: [2-(3-Bromophenylamino)-4-trifluoromethylpyrimidin-5-yl]-piperidin-4-yl-methanone

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In a manner similar to Reference Example 1(c) 2-(3-bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and piperidine (12 μ l) afforded the title compound (31 mg).

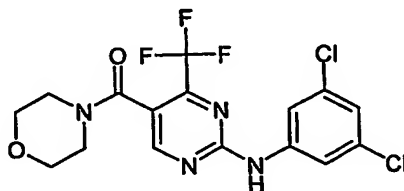
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NMR (DMSO- d_6) δ 1.3-1.7 (6H, m), 3.26 (2H, s), 3.60 (2H, br s), 7.21 (1H, d), 7.30 (1H, t), 7.70 (1H, d), 8.11 (1H, s), 8.78 (1H, s), 10.55 (1H, s).

LC/MS, $t = 3.57$ min, $[MH^+]$ 429 and 431.

Example 13: 2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-morpholin-4-yl-methanone

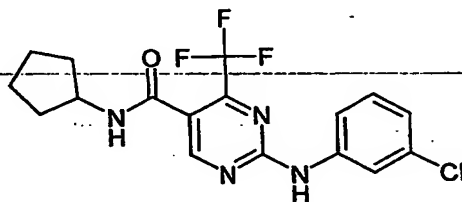
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In a manner similar to Reference Example 1(c) 2-(3,5-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and morpholine (14.5 μ l) afforded the title compound (42 mg).

10 NMR (DMSO- d_6) δ 3.4-3.75 (8H, m), 7.35 (1H, s), 7.89 (2H, s), 8.87 (1H, s), 10.80 (1H, s).
LC/MS, $t = 3.52$ min, $[MH^+]$ 421 and 423.

Example 14: 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-carboxylic acid N-cyclopentylamide

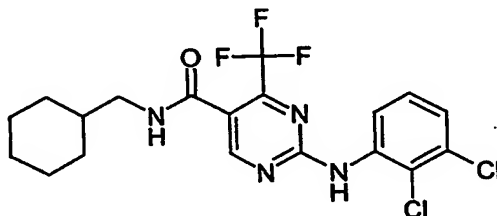


15

In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and cyclopentylamine (13 μ l) afforded the title compound (34 mg).

20 NMR (DMSO- d_6) δ 1.5 (4H, m), 1.65 (2H, m), 1.85 (2H, m), 4.15 (1H, m), 7.09 (1H, d), 7.36 (1H, t), 7.67 (1H, d), 7.97 (1H, s), 8.55 (1H, d), 8.79 (1H, s), 10.60 (1H, s).
LC/MS, $t = 3.55$ min, $[MH^+]$ 385 and 387.

Example 15: 2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclohexylmethyl)amide



25

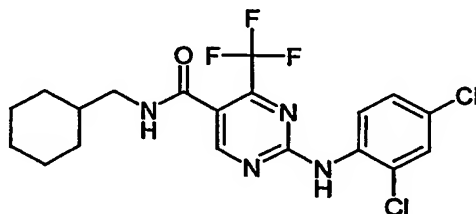
In a manner similar to Reference Example 1(c) 2-(2,3-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and cyclohexanemethylamine (16 μ l) afforded the title compound (30 mg).

30 NMR (DMSO- d_6) δ 0.85-1.0 (2H, m), 1.1-1.3 (3H, m), 1.45 (1H, m), 1.55-1.8 (5H, m), 3.05 (2H, t), 7.40 (1H, t), 7.55 (2H, d), 8.53 (1H, t), 8.65 (1H, s), 10.15 (1H, s).

LC/MS, $t = 3.84$ min, $[MH^+]$ 447 and 449.

Example 16: 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclohexylmethyl)amide

5

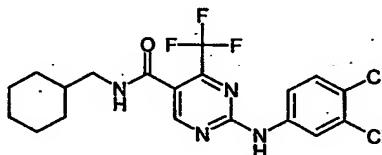


In a manner similar to Reference Example 1(c) 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and cyclohexanemethylamine (16 μ l) afforded the title compound (14 mg).

- 10 NMR (DMSO- d_6) δ 0.85-1.0 (2H, m), 1.1-1.3 (3H, m), 1.45 (1H, m), 1.55-1.75 (5H, m), 3.05 (2H, t), 7.46 (1H, d), 7.57 (1H, d), 7.72 (1H, s), 8.53 (1H, t), 8.64 (1H, s), 10.00 (1H, s).
LC/MS, $t = 3.90$ min, $[MH^+]$ 447 and 449.

Example 17: 2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclohexylmethyl)amide

15

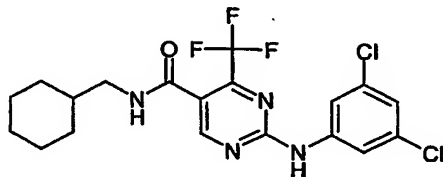


In a manner similar to Reference Example 1(c) 2-(3,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and cyclohexanemethylamine (16 μ l) afforded the title compound (31 mg).

- 20 NMR (DMSO- d_6) δ 0.8-1.0 (2H, m), 1.1-1.3 (3H, m), 1.5 (1H, m), 1.55-1.8 (5H, m), 3.06 (2H, t), 7.62 (1H, d), 7.69 (1H, d), 8.18 (1H, s), 8.59 (1H, t), 8.82 (1H, s), 10.70 (1H, s).
LC/MS, $t = 4.01$ min, $[MH^+]$ 447 and 449.

Example 18: 2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclohexylmethyl)amide

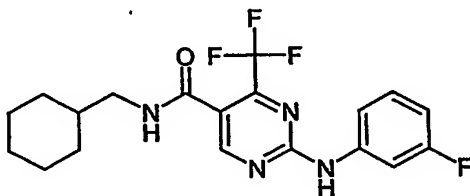
25



In a manner similar to Reference Example 1(c) 2-(3,5-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and cyclohexanemethylamine (16 μ l) afforded the title compound (30 mg).

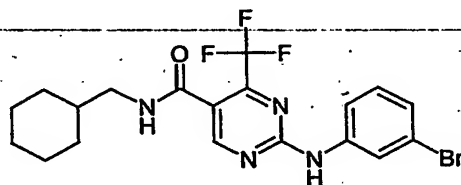
- 30 NMR (DMSO- d_6) δ 0.85-1.0 (2H, m), 1.1-1.3 (3H, m), 1.5 (1H, m), 1.55-1.8 (5H, m), 3.07 (2H, t), 7.26 (1H, s), 7.89 (2H, s), 8.58 (1H, t), 8.86 (1H, s), 10.80 (1H, s).
LC/MS, $t = 4.08$ min, $[MH^+]$ 447 and 449.

Example 19: 2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclohexylmethyl)amide



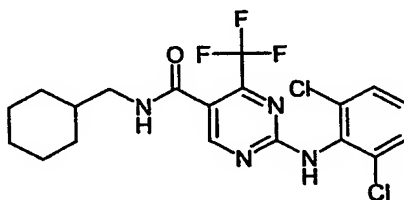
- 5 In a manner similar to Reference Example 1(c) 2-(3-fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and cyclohexanemethylamine (18 μ l) afforded the title compound (38 mg).
NMR (DMSO- d_6) δ 0.85-1.0 (2H, m), 1.1-1.3 (3H, m), 1.5 (1H, m), 1.55-1.8 (5H, m), 3.09 (2H, t), 6.87 (1H, t of d), 7.39 (1H, q), 7.53 (1H, d), 7.78 (1H, d of t), 8.59 (1H, t), 8.80 (1H, s), 10.60 (1H, s).
10 LC/MS, $t = 3.68$ min, $[MH^+]$ 397.

Example 20: 2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclohexylmethyl)amide



- 15 In a manner similar to Reference Example 1(c) 2-(3-bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and cyclohexanemethylamine (15 μ l) afforded the title compound (36 mg).
20 NMR (DMSO- d_6) δ 0.85-1.0 (2H, m), 1.1-1.3 (3H, m), 1.5 (1H, m), 1.55-1.8 (5H, m), 3.08 (2H, t), 7.23 (1H, d), 7.31 (1H, t), 7.71 (1H, d), 8.10 (1H, s), 8.57 (1H, t), 8.80 (1H, s), 10.60 (1H, s).
LC/MS, $t = 3.85$ min, $[MH^+]$ 457 and 459.

Example 21: 2-(2,6-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclohexylmethyl)amide

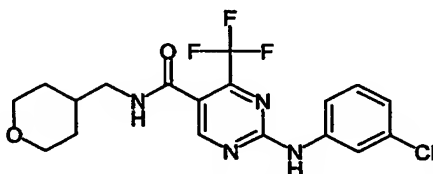


- 25 In a manner similar to Reference Example 1(c) 2-(2,6-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (33 mg) and cyclohexanemethylamine (15 μ l) afforded the title compound (9 mg).
30

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.05-1.25 (3H, m), 1.46 (1H, m), 1.55-1.8 (5H, m), 3.04 (2H, t), 7.39 (1H, t), 7.59 (2H, d), 8.56 (2H, m), 10.10 (1H, s).

LC/MS, $t = 3.84$ min, $[MH^+]$ 447 and 449.

5 Example 22: 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydro-pyran-4-ylmethyl)amide

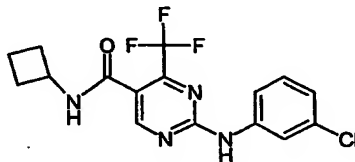


- 10 In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (30 mg) and 4-aminomethyltetrahydropyran (13 mg) afforded the title compound (25 mg).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.62 (2H, d), 1.74 (1H, m), 3.13 (2H, t), 3.27 (2H, t), 3.86 (2H, d), 7.10 (1H, d), 7.37 (1H, t), 7.66 (1H, d), 7.97 (1H, s), 8.63 (1H, t), 8.82 (1H, s), 10.60 (1H, s).

- 15 LC/MS, $t = 3.22$ min, $[MH^+]$ 415 and 417.

Example 23: 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-carboxylic acid N-(cyclobutyl)amide



- 20 In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and cyclobutylamine (10 μ l) afforded the title compound (28 mg).

NMR (DMSO-d₆) δ 1.6-1.75 (2H, m), 1.9-2.05 (2H, m), 2.2-2.3 (2H, m), 4.32 (1H, m), 7.10 (1H, d), 7.37 (1H, t), 7.67 (1H, d), 7.96 (1H, s), 8.82 (2H, s), 10.60 (1H, s).

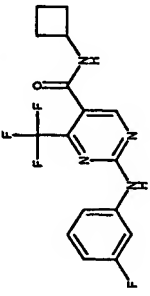
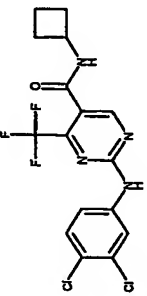
- 25 LC/MS, $t = 3.45$ min, $[MH^+]$ 371 and 373.

Examples 24 to 30

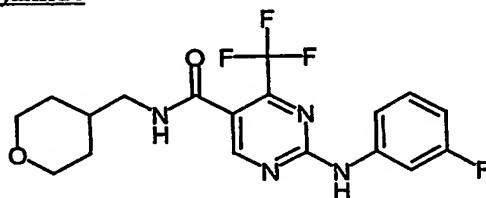
- 30 Table 1) gives examples 24 to 30, column 1 gives the precursors that were reacted with methyl 2-chloro-4-trifluoromethylpyrimidine-5-carboxylate in a manner similar to that in Reference example 1(a). In a manner similar to that in Reference example 1(b), the carboxylic acid of the resultant ester was prepared. Finally, in a manner similar to that of Reference example 1(c), the resultant acid product was reacted with the precursor of column 2 to provide the final product of column 3.

Table 1

Ex	1	2	3 - Product	Structure	LC/MS 1 Retention time (min) 2 MH ⁺ 3 Formula
24	Aniline	Piperidine	1-(2-Phenylamino-4-trifluoromethyl-pyrimidin-5-yl)-1-piperidin-1-yl-methanone		3.38 351 C ₁₇ H ₁₇ F ₃ N ₄ O
25	Aniline	Morpholine	1-Morpholin-4-yl-1-(2-phenylamino-4-trifluoromethyl-pyrimidin-5-yl)-methanone		3.04 353 C ₁₆ H ₁₃ F ₃ N ₄ O ₂
26	3-Chloroaniline	Aminoacetoneitrile	2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (cyanomethyl)-amide		3.27 356 C ₁₄ H ₉ ³⁵ Cl F ₃ N ₅ O
27	3-Chloroaniline	3,3-Dimethylbutyl amine	2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (3,3-dimethyl-butyl)-amide		3.80 401 C ₁₈ H ₂₀ ³⁵ Cl F ₃ N ₄ O
28	3-Chloroaniline	Neopentylamine	2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (2,2-dimethyl-propyl)-amide		3.69 387 C ₁₇ H ₁₈ ³⁵ Cl F ₃ N ₄ O

29	3-Fluoroaniline	Cyclobutylamine	2-(3-Fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylamide		3.29 355 $C_{16}H_{14}F_4N_4O$
30	3,4-Dichloroaniline	Cyclobutylamine	2-(3,4-Dichloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylamide		3.66 405 $C_{16}H_{13}^{35}Cl_2F_3N_4O$

Example 31: 2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydropyran-4-ylmethyl)amide

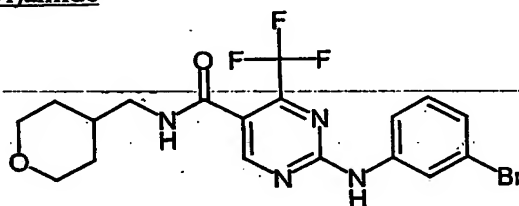


- 5 In a manner similar to Reference Example 1(c) 2-(3-fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and 4-aminomethyltetrahydropyran (16 mg) afforded the title compound (38 mg).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.63 (2H, d), 1.75 (1H, m), 3.15 (2H, t), 3.29 (2H, t), 3.86 (2H, d), 6.88 (1H, td), 7.38 (1H, q), 7.51 (1H, d), 7.76 (1H, dt), 8.64 (1H, t), 8.82 (1H, s), 10.60 (1H, s).

LC/MS, $t = 3.08$ min, $[MH^+]$ 399.

Example 32: 2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydropyran-4-ylmethyl)amide

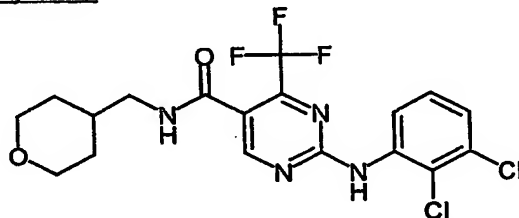


- 15 In a manner similar to Reference Example 1(c) 2-(3-bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and 4-aminomethyltetrahydropyran (13.5 mg) afforded the title compound (36 mg).

20 NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.62 (2H, d), 1.74 (1H, m), 3.13 (2H, t), 3.27 (2H, t), 3.86 (2H, d), 7.23 (1H, d), 7.31 (1H, t), 7.71 (1H, d), 8.11 (1H, s), 8.63 (1H, t), 8.82 (1H, s), 10.60 (1H, s).

LC/MS, $t = 3.26$ min, $[MH^+]$ 459 and 461.

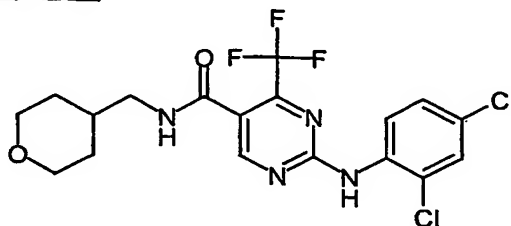
Example 33: 2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydropyran-4-ylmethyl)amide



In a manner similar to Reference Example 1(c) 2-(2,3-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (30 mg) and 4-aminomethyltetrahydropyran (12 mg) afforded the title compound (25 mg).

NMR (DMSO-d₆) δ 1.1-1.25 (2H, m), 1.60 (2H, d), 1.72 (1H, m), 3.11 (2H, t), 3.26 (2H, t), 3.85 (2H, d), 7.40 (1H, t), 7.55 (2H, d), 8.60 (1H, t), 8.66 (1H, s), 10.10 (1H, s).
LC/MS, $t = 3.29$ min, $[MH^+]$ 449 and 451.

5 Example 34: 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydropyran-4-ylmethyl)amide

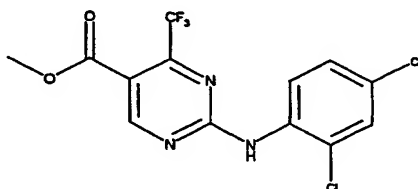


10 In a manner similar to Reference Example 1(c) 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (30 mg) and 4-aminomethyltetrahydropyran (12 mg) afforded the title compound (34 mg).

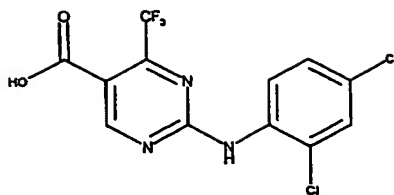
NMR (DMSO-d₆) δ 1.1-1.25 (2H, m), 1.59 (2H, d), 1.72 (1H, m), 3.11 (2H, t), 3.26 (2H, t), 3.85 (2H, d), 7.47 (1H, dd), 7.57 (1H, d), 7.72 (1H, s), 8.60 (1H, t), 8.65 (1H, s), 10.05 (1H, s).
LC/MS, $t = 3.33$ min, $[MH^+]$ 449 and 451.

15 Additional synthesis of Example 34: 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydro-pyran-4-ylmethyl)amide

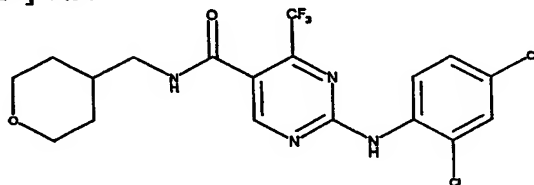
(a). To a solution of methyl 2-chloro-4-trifluoromethylpyrimidine-5-carboxylate (0.50 g, ex Maybridge) in 1,4-dioxan (5 ml) was added 2,4-dichloroaniline (1.7 g) and the solution stirred under reflux for 7 h. 1,4-Dioxan was removed under reduced pressure and ethyl acetate (15 ml) added. The solution was washed sequentially with 2N hydrochloric acid (10 ml) and water (3 x 10 ml), dried (MgSO₄), evaporated and triturated with hexane to afford methyl 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylate (358 mg).
NMR (CDCl₃) δ 3.95 (3H, s), 7.30 (1H, dd), 7.45 (1H, d), 8.00 (1H, s), 8.5 (1H, d), 9.05 (1H, s).
25 LC/MS, $t = 3.74$ min, $[MH^+]$ 366.



(b). To a solution of methyl 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylate (0.358 g) in ethanol (8 ml) was added a solution of potassium hydroxide (190 mg) in ethanol (8 ml) and the solution stirred at reflux for 24 h. Ethanol was removed under reduced pressure and water (15 ml) added. The solution was washed with ether and concentrated hydrochloric acid was added to adjust the acidity to pH 1. The precipitated solid was filtered, washed with water and dried in vacuo at 50°C to afford 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (262 mg).
35 NMR (DMSO-d₆) δ 7.48 (1H, dd), 7.60 (1H, d), 7.73 (1H, d), 8.95 (1H, s), 10.3 (1H, s), 13.6 (1H, s).



- (c). To a solution of 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30 mg) in dimethylformamide (2 ml) was added successively N-ethylmorpholine (33 μ l), 4-aminomethyltetrahydropyran (12mg), 1-hydroxybenzotriazole hydrate (18 mg) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (20 mg). The solution was stirred for 3 h and allowed to stand overnight. Dimethylformamide was removed under reduced pressure and ethyl acetate (5 ml) added. The solution was washed sequentially with 5% sodium bicarbonate solution (2.5 ml), water (2.5 ml), 5% citric acid solution (2.5 ml) and brine (2 x 2.5 ml), dried (MgSO_4) and evaporated to afford the title compound (34 mg) NMR (DMSO-d_6) δ 1.20 (2H, m), 1.58 (2H, d), 1.70 (1H, m), 3.10 (2H, t), 3.23 (2H, t), 3.84 (2H, dd), 7.46 (1H, dd), 7.57 (1H, d), 7.71 (1H, d), 8.59 (1H, t), 8.63 (1H, s), 10.00 (1H, s). LC/MS, $t = 3.33$ min, $[\text{MH}^+]$ 449.



15 Additional synthesis of Example 34: 2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid N-(tetrahydro-pyran-4-ylmethyl)amide

- (a). To a solution of methyl 2-chloro-4-trifluoromethylpyrimidine-5-carboxylate (70 g, ex Maybridge 22g, ex Fluorochem 48g) in 1,4-dioxan (100 ml) was added 2,4-dichloroaniline (142 g) and the solution stirred under reflux for 10.5 h. 1,4-Dioxan was partially removed (approx 50ml) under reduced pressure and 2N HCl (800ml) added. The mixture was stirred with overhead stirring for 3h and the resulting solid filtered onto a sinter. The solid was washed with 2N HCl (2 x 300ml) and water (4 x 400ml) then dried over sodium hydroxide in vacuo at 50°C to afford methyl 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylate. The solid contained approximately 5% 2,4-dichloroaniline. NMR (DMSO-d_6) δ 3.84 (3H, s), 7.47 (1H, dd), 7.49 (1H, d), 7.74 (1H, d), 8.96 (1H, s), 10.45 (1H, s). LC/MS, $t = 3.66$ min, $[\text{MH}^+]$ 366.

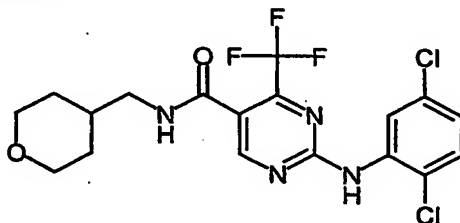
- (b). To a solution of methyl 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylate (107 g) in methanol (700 ml) was added a solution of potassium hydroxide (50 g) in methanol (700 ml) and the solution stirred at reflux for 24 h. Methanol was removed under reduced pressure and water (800 ml) added. The solution was washed with ether (3 x 400 ml, which removed the remaining 2,4-dichloroaniline) and concentrated hydrochloric acid added to adjust the acidity to pH 1. The precipitated solid was filtered, washed with 2N HCl and water until the pH of the filtrate was neutral. The solid was dried in vacuo at 50°C to afford 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (86.9 g)

NMR (DMSO-d₆) δ 7.48 (1H, dd), 7.60 (1H, d), 7.73 (1H, d), 8.95 (1H, s), 10.3 (1H, s), 13.6 (1H, s).

LC/MS, $t = 4.35$ min, $[MH^+]$ 352

- 5 (c). To a solution of 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (86 g) in dimethylformamide (800 ml) was added successively N-ethylmorpholine (93ml), 4-aminomethyltetrahydropyran (29.5g), 1-hydroxybenzotriazole hydrate (51.5g) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (56.2g). The solution was stirred for 24h. Dimethylformamide was partially removed (approx 650ml) under reduced pressure and 5% sodium bicarbonate solution added (3 x 500 ml, added portionwise to control the release of carbon dioxide). The mixture was stirred with overhead stirring for 3h and the resulting solid filtered onto a sinter. The solid was washed with 5% sodium bicarbonate (4 x 400ml) and water (3 x 400ml) then dried over sodium hydroxide in vacuo at 50°C to afford the title compound (109.1g)
- 10
- 15 NMR (DMSO-d₆) δ 1.20 (2H, m), 1.58 (2H, d), 1.70 (1H, m), 3.10 (2H, t), 3.23 (2H, t), 3.84 (2H, dd), 7.46 (1H, dd), 7.57 (1H, d), 7.71 (1H, d), 8.59 (1H, t), 8.63 (1H, s), 10.00 (1H, s). LC/MS, $t = 3.41$ min, $[MH^+]$ 449.

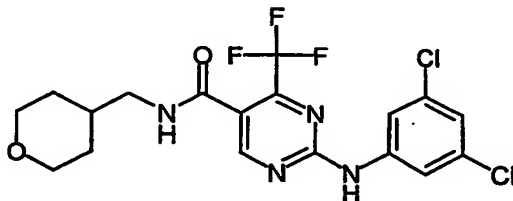
20 Example 35: 2-(2,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydropyran-4-ylmethyl)amide



In a manner similar to Reference Example 1(c) 2-(2,5-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (50 mg) and 4-aminomethyltetrahydropyran (25 mg) afforded the title compound (63 mg).

- 25 NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.60 (2H, d), 1.72 (1H, m), 3.12 (2H, t), 3.27 (2H, t), 3.85 (2H, d), 7.35 (1H, dd), 7.59 (1H, d), 7.73 (1H, s), 8.62 (1H, t), 8.70 (1H, s), 10.05 (1H, s). LC/MS, $t = 3.30$ min, $[MH^+]$ 449 and 451.

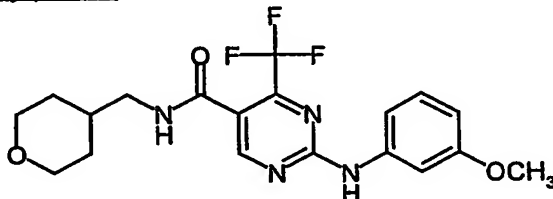
30 Example 36: 2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydropyran-4-ylmethyl)amide



- 35 In a manner similar to Reference Example 1(c) 2-(3,5-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (50 mg) and 4-aminomethyltetrahydropyran (25 mg) afforded the title compound (68 mg).

NMR (DMSO-d₆) δ 1.15-1.35 (2H, m), 1.62 (2H, d), 1.72 (1H, m), 3.14 (2H, t), 3.28 (2H, t), 3.86 (2H, d), 7.25 (1H, s), 7.88 (2H, s), 8.66 (1H, t), 8.88 (1H, s), 10.75 (1H, s).

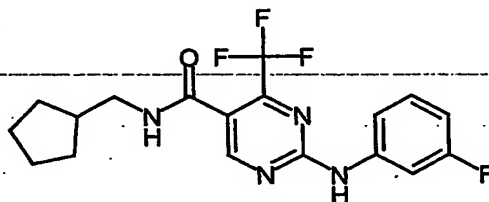
Example 37: 2-(3-Methoxyphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(tetrahydropyran-4-ylmethyl)amide



In a manner similar to Reference Example 1(c) 2-(3-methoxyphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and 4-aminomethyltetrahydropyran (14.5 mg) afforded the title compound (29 mg).

- 10 NMR (DMSO-d₆) δ 1.1-1.25 (2H, m), 1.61 (2H, d), 1.74 (1H, m), 3.13 (2H, t), 3.27 (2H, t), 3.74 (3H, s), 3.86 (2H, d), 6.63 (1H, d), 7.25 (2H, m), 7.53 (1H, s), 8.62 (1H, t), 8.76 (1H, s), 10.35 (1H, s).
LC/MS, $t = 2.97$ min, $[MH^+]$ 411.

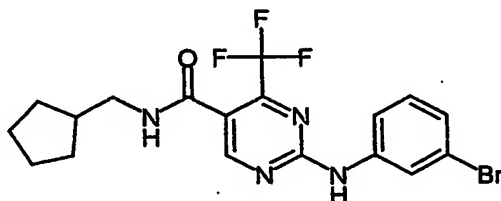
Example 38: 2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide



In a manner similar to Reference Example 1(c) 2-(3-fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (30 mg) and cyclopentylmethylamine hydrochloride (17 mg, prepared as described in Kelley et al., J. Med. Chem., **40**, 3207, (1997)) afforded the title compound (17 mg).

- 20 NMR (DMSO-d₆) δ 1.20-1.30 (2H, m), 1.45-1.68 (4H, m), 1.68-1.77 (2H, m), 2.1 (1H, quintuplet), 3.19 (2H, t), 6.89 (1H, dt), 7.40 (1H, q), 7.54 (1H, d), 7.78 (1H, d), 8.64 (1H, t), 8.80 (1H, s), 10.70 (1H, s).
LC/MS, $t = 3.53$ min, $[MH^+]$ 383.

Example 39: 2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide



In a manner similar to Reference Example 1(c) 2-(3-bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (36.5 mg) and cyclopentylmethylamine hydrochloride (17 mg) afforded the title compound (28 mg).

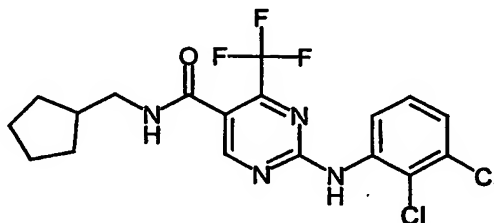
30

NMR (DMSO-d₆) δ 1.39-1.52 (2H, m), 1.69-1.90 (4H, m), 1.90- 2.02 (2H, m), 2.34 (1H, quintuplet), 3.4 (2H, t), 7.48 (1H, d), 7.57 (1H, t), 7.95 (1H, d), 8.37 (1H, s). 8.86 (1H, t), 9.02 (1H, s), 10.80 (1H, s).

LC/MS, $t = 3.33$ min, $[MH^+]$ 443 and 445.

5

Example 40: 2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide



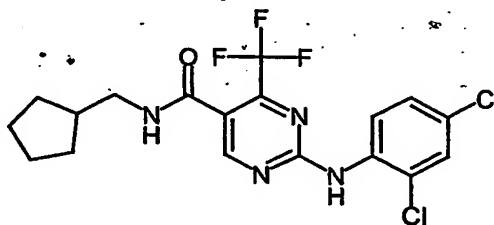
In a manner similar to Reference Example 1(c) 2-(2,3-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclopentylmethylamine hydrochloride (15 mg) afforded the title compound (30 mg).

NMR (DMSO-d₆) δ 1.15-1.30 (2H, m), 1.44-1.78 (6H, m), 2.10 (1H, quintuplet), 3.16 (2H, t), 7.41 (2H, t), 7.54 (1H, m), 8.58 (1H, br t), 8.78 (1H, s), 10.10 (1H, s).

LC/MS, $t = 3.71$ min, $[MH^+]$ 433 and 435.

15

Example 41: 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide



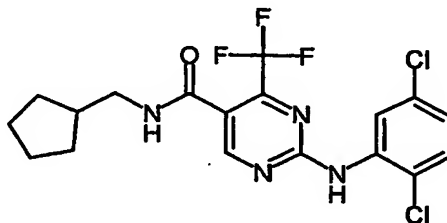
In a manner similar to Reference Example 1(c) 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclopentylmethylamine hydrochloride (15 mg) afforded the title compound (27 mg).

NMR (DMSO-d₆) δ 1.2-1.3 (2H, m), 1.4-1.79 (6H, m), 2.10 (1H, quintuplet), 3.17 (2H, t), 7.50 (1H, d), 7.60 (1H, d), 7.75 (1H, d), 8.68 (1H, t), 8.78 (1H, s), 10.10 (1H, s).

LC/MS, $t = 3.76$ min, $[MH^+]$ 433 and 435.

25

Example 42: 2-(2,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide

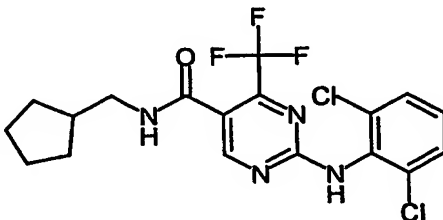


In a manner similar to Reference Example 1(c) 2-(2,5-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclopentylmethylamine hydrochloride (15 mg) afforded the title compound (23 mg).

NMR (DMSO-d₆) δ 1.15-1.30 (2H, m), 1.45-1.79 (6H, m), 2.08 (1H, quintuplet), 3.18 (2H, t), 7.38 (1H, d), 7.62 (1H, d), 7.75 (1H, s), 8.61 (1H, br t), 8.71 (1H, s), 10.05 (1H, s).

LC/MS, $t = 3.76$ min, $[MH^+]$ 433 and 435.

Example 43: 2-(2,6-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide

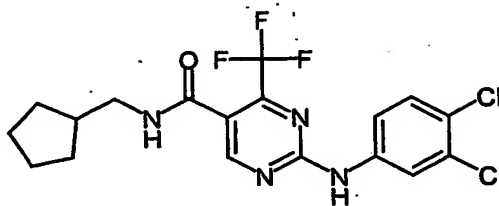


In a manner similar to Reference Example 1(c) 2-(2,6-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclopentylmethylamine hydrochloride (15 mg) afforded the title compound (25 mg).

NMR (DMSO-d₆) δ 1.15-1.30 (2H, m), 1.45-1.78 (6H, m), 2.08 (1H, quintuplet), 3.15 (2H, t), 7.4 (1H, t), 7.6-7.68 (2H, m), 8.5-8.7 (2H, m), 10.20 (1H, s).

LC/MS, $t = 3.49$ min, $[MH^+]$ 433 and 435.

Example 44: 2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide

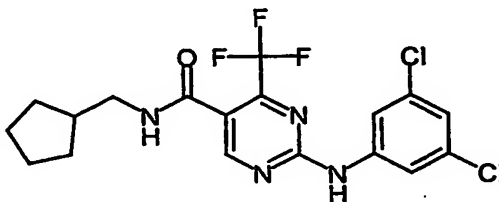


In a manner similar to Reference Example 1(c) 2-(3,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclopentylmethylamine hydrochloride (15 mg) afforded the title compound (29 mg).

NMR (DMSO-d₆) δ 1.12-1.3 (2H, m), 1.44-1.8 (6H, m), 2.1 (1H, quintuplet), 3.17 (2H, t), 7.62 (1H, br d), 7.72 (1H, d), 8.18 (1H, d), 8.60-8.69 (1H, br t), 8.83 (1H, s), 10.80 (1H, s).

LC/MS, $t = 3.87$ min, $[MH^+]$ 433 and 435.

Example 45: 2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide

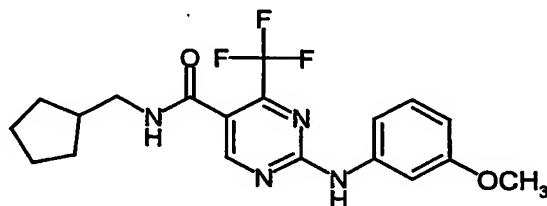


In a manner similar to Reference Example 1(c) 2-(3,5-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclopentylmethylamine hydrochloride (15 mg) afforded the title compound (27 mg).

NMR (DMSO-d₆) 1.14-1.34 (2H, m), 1.45-1.8 (6H, m), 2.10 (1H, quintuplet), 3.20 (2H, t), 7.28 (1H, s), 7.91 (2H, s), 8.6-8.7 (1H, br t), 8.9 (1H, s), 10.75 (1H, s).

LC/MS, t = 3.94 min, [MH⁺] 433 and 435.

Example 46: 2-(3-Methoxyphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclopentylmethyl)amide

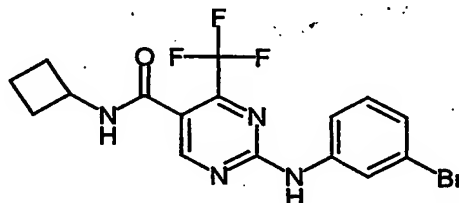


In a manner similar to Reference Example 1(c) 2-(3-methoxyphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclopentylmethylamine hydrochloride (17 mg) afforded the title compound (21 mg).

NMR (DMSO-d₆) 1.25-1.38 (2H, m), 1.50-1.85 (6H, m), 2.15 (1H, quintuplet), 3.25 (2H, t), 3.85 (3H, s), 6.70 (1H, br d), 7.26-7.37 (2H, m), 7.60 (1H, m), 8.68 (1H, t), 8.80 (1H, s), 10.50 (1H, s).

LC/MS, t = 3.46 min, [MH⁺] 395.

Example 47: 2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-cyclobutylamide

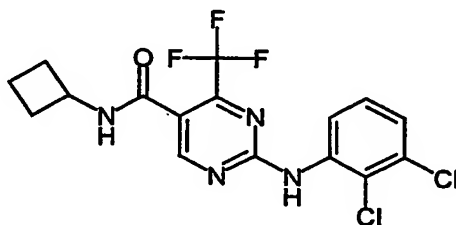


In a manner similar to Reference Example 1(c) 2-(3-bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and cyclobutylamine (10 µl) afforded the title compound (30 mg).

NMR (DMSO-d₆) δ 1.70 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 4.32 (1H, m), 7.22-7.33 (2H, m), 7.70 (1H, d), 8.10 (1H, s), 8.81-8.83 (2H, m), 10.60 (1H, s).

LC/MS, t = 3.47 min, [MH⁺] 415 and 417.

Example 48: 2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid -cyclobutylamide



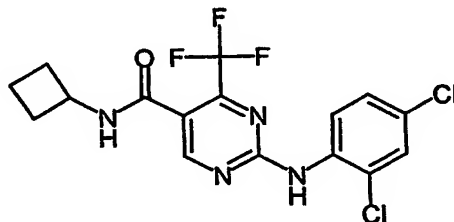
In a manner similar to Reference Example 1(c) 2-(2,3-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (25 mg) and cyclobutylamine (10 μ l) afforded the title compound (20 mg).

NMR (DMSO-d₆) δ 1.70 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 4.32 (1H, m), 7.38-7.56 (3H, m),

5 8.65 (1H, s), 8.80 (1H, d), 10.10 (1H, s).

LC/MS, $t = 3.48$ min, $[MH^+]$ 405 and 407.

Example 49: 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-cyclobutylamide



10

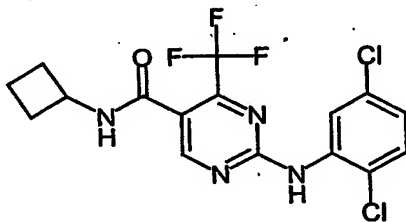
In a manner similar to Reference Example 1(c) 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (30 mg) and cyclobutylamine (10 μ l) afforded the title compound (26 mg).

NMR (DMSO-d₆) δ 1.70 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 4.32 (1H, m), 7.46-7.72 (3H, m),

15 8.64 (1H, s), 8.80 (1H, d), 10.00 (1H, s).

LC/MS, $t = 3.54$ min, $[MH^+]$ 405 and 407.

Example 50: 2-(2,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-cyclobutylamide



20

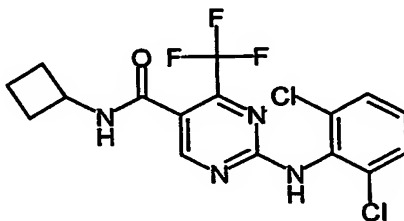
In a manner similar to Reference Example 1(c) 2-(2,5-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (50 mg) and cyclobutylamine (19 μ l) afforded the title compound (56 mg).

NMR (DMSO-d₆) δ 1.70 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 4.30 (1H, m), 7.33-7.73 (3H, m),

25 8.70 (1H, s), 8.80 (1H, d), 10.00 (1H, s).

LC/MS, $t = 3.52$ min, $[MH^+]$ 405 and 407.

Example 51: 2-(2,6-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-cyclobutylamide

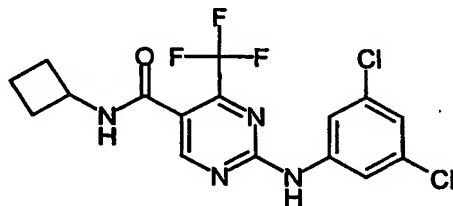


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In a manner similar to Reference Example 1(c) 2-(2,6-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (30 mg) and cyclobutylamine (10 μ l) afforded the title compound (34 mg).

5 NMR (DMSO- d_6) δ 1.70 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 4.30 (1H, m), 7.36-7.60 (3H, m), 8.59 (1H, s), 8.80 (1H, d), 10.15 (1H, s).
LC/MS, $t = 3.24$ min, $[MH^+]$ 405 and 407.

Example 52: 2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-cyclobutylamide

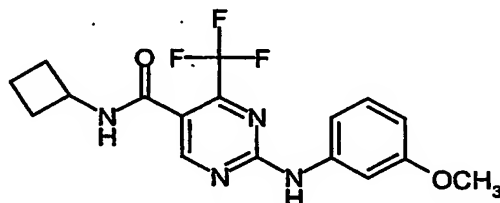


10

In a manner similar to Reference Example 1(c) 2-(3,5-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (50 mg) and cyclobutylamine (19 μ l) afforded the title compound (56 mg).

15 NMR (DMSO- d_6) δ 1.70 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 4.32 (1H, m), 7.25-7.87 (3H, m), 8.85 (1H, d), 8.88 (1H, s), 10.80 (1H, s).
LC/MS, $t = 3.73$ min, $[MH^+]$ 405 and 407.

Example 53: 2-(3-Methoxyphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-cyclobutylamide



20

In a manner similar to Reference Example 1(c) 2-(3-methoxyphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclobutylamine (10.5 μ l) afforded the title compound (27 mg).

25 NMR (DMSO- d_6) δ 1.70 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 3.75 (3H, s), 4.32 (1H, m), 7.53-7.87 (4H, m), 8.76 (1H, s), 8.81 (1H, d), 10.40 (1H, s).
LC/MS, $t = 3.20$ min, $[MH^+]$ 367.

Example 54: 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-(cyclobutylmethyl)amide

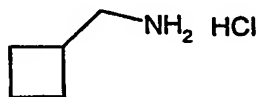
30

(a) A solution of borane-tetrahydrofuran complex (1M in tetrahydrofuran, 120ml) was added over 10min to a solution of cyclobutane carbonitrile (8.1g) [Lancaster] in dry tetrahydrofuran (20ml) under nitrogen at room temperature. The solution was refluxed overnight then cooled to 20°. Methanol (150ml) was added dropwise over 15mins keeping the temperature below 25°, then the mixture was cooled to 0° and dry hydrogen chloride was bubbled through for 30min. The resulting mixture was refluxed for 90min, evaporated and the residue re-evaporated twice from

35

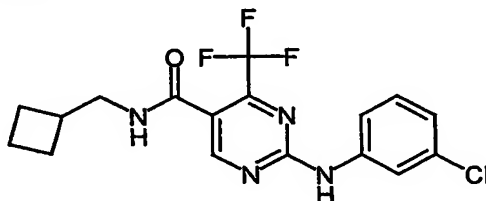
methanol. Ether (150ml) was added and the resulting solid was filtered off. It was taken up in hot isopropanol (50ml), filtered, and hot acetonitrile (30ml) added. The mixture was cooled and the solid filtered off to give the C-cyclobutylmethylamine hydrochloride (5.7g)

NMR (400 MHz, DMSO-d₆) δ 1.8 (4H, m), 2.0 (2H, m), 2.54 (1H, m), 2.80 (2H, d), 8.0 (3H, br s).

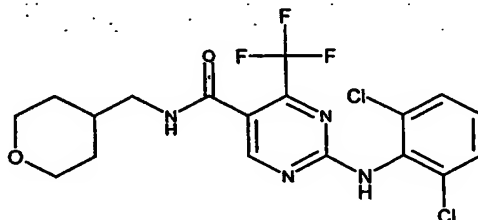


(b) In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and C-cyclobutylmethylamine hydrochloride (13 mg) afforded the title compound (28 mg).

10 NMR (DMSO-d₆) δ 1.70 (2H, m), 1.82 (2H, m), 2.00 (2H, m), 2.50 (1H, m), 3.26 (2H, m), 7.08-7.95 (4H, m), 8.55 (1H, t), 8.77 (1H, s), 10.60 (1H, s).
LC/MS, t_r = 3.56 min, $[MH^+]$ 385.



15 Example 55: 2-(2,6-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)amide



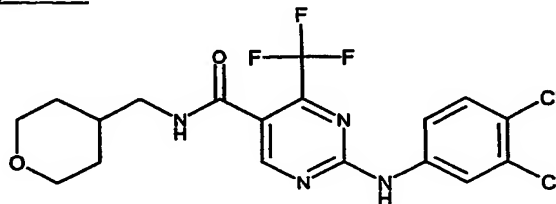
20 In a manner similar to Reference Example 1(c) 2-(2,6-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (30mg) and 4-aminomethyltetrahydropyran (20mg, ex CombiBlocks) afforded the title compound (32mg).

NMR (DMSO-d₆) δ 1.16-1.22 (2H, m), 1.58 (2H, d), 1.70 (1H, m), 3.09 (2H, t), 3.23 (2H, m), 3.84 (2H, d), 7.38 (1H, t), 7.59 (2H, d), 8.61 (2H, m), 10.10 (1H, s)

LC/MS, t_r = 3.02 min, Molecular ion observed (MH^+) = 449 consistent with the molecular formula

25 $C_{18}H_{17}^{35}Cl_2F_3N_4O_2$

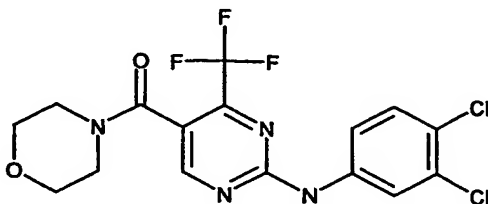
Example 56: 2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Reference Example 1(c) 2-(3,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (30mg) and 4-aminomethyltetrahydropyran (20mg, ex CombiBlocks) afforded the title compound (38mg).

NMR (DMSO-d₆) δ 1.18-1.25 (2H, m), 1.62 (2H, d), 1.74 (1H, m), 3.1 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.60 (1H, t), 7.69 (1H, m), 8.16 (1H, dd), 8.64 (1H, t), 8.84 (1H, s), 10.70 (1H, s)
LC/MS, t = 3.45 min, Molecular ion observed (MH⁺) = 449 consistent with the molecular formula C₁₈H₁₇N₄O₂³⁵Cl₂F₃

Example 68: 1-{2-[(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]}-1-(morpholin-4-yl)-methanone



In a manner similar to Reference Example 1(c) 2-(3,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (30mg) and morpholine (15mg, ex Aldrich) afforded the title compound (36mg).

NMR (DMSO-d₆) δ 3.7 (8H, s), 7.65 (1H, d), 7.75 (1H, dd), 8.2 (1H, d), 8.9 (1H, s), 10.80 (1H, s)

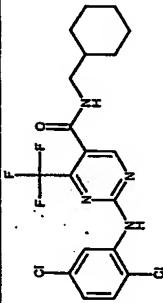
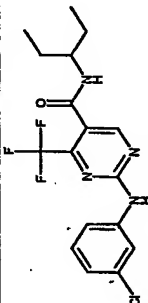
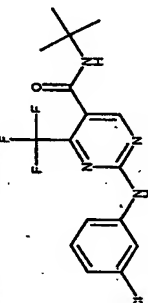
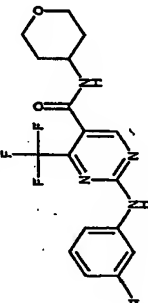
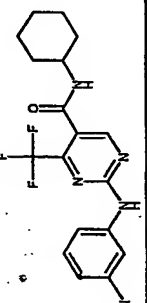
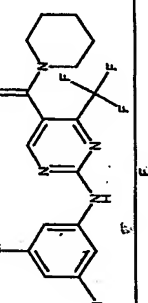
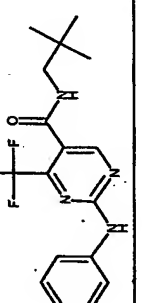
LC/MS, t = 3.45 min, Molecular ion observed (MH⁺) = 421 consistent with the molecular formula C₁₆H₁₃N₄O₂³⁵Cl₂F₃

Table 2:

Example 57-67 and 69-73 were prepared in a corresponding fashion to the above compounds.

Table 2

Compound Name	Structure	Mass spec details 1 Retention Time 2 MH ⁺ 3 Formula consistent with MH ⁺
57 2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cycloheptylamide		3.78 413 C ₁₉ H ₂₀ ³⁵ ClF ₃ N ₄ O
58 2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid [(S)-1-(tetrahydro-furan-2-yl)methyl]-amide		3.25 401 C ₁₇ H ₁₆ ³⁵ ClF ₃ N ₄ O ₂
59 2-(3-Fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid [(S)-1-(tetrahydro-furan-2-yl)methyl]-amide		3.10 385 C ₁₇ H ₁₆ F ₄ N ₄ O ₂
60 2-(3-Bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid [(S)-1-(tetrahydro-furan-2-yl)methyl]-amide		3.29 447 C ₁₇ H ₁₆ ⁸¹ BrF ₃ N ₄ O ₂
61 2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (1-methanesulfonyl-piperidin-4-ylmethyl)-amide		3.22 492 C ₁₉ H ₂₁ ³⁵ ClF ₃ N ₅ O ₃ S

62	2-(2,5-Dichloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		3.90 447 $C_{19}H_{19}^{35}Cl_2F_3N_4O$
63	2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (1-ethyl-propyl)-amide		3.60 387 $C_{17}H_{18}^{35}ClF_3N_4O$
64	2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tert-butyl)-amide		3.55 373 $C_{16}H_{16}^{35}ClF_3N_4O$
65	2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-yl)-amide		3.18 401 $C_{17}H_{16}^{35}ClF_3N_4O_2$
66	2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexyl-amide		3.67 399 $C_{18}H_{18}^{35}ClF_3N_4O$
67	1-[2-(3,5-Dichloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-1-(piperidin-1-yl)-methanone		3.84 419 $C_{17}H_{15}^{35}Cl_2F_3N_4O$
69	2-Phenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid (2,2-dimethyl-propyl)-amide		3.48 353 $C_{17}H_{19}F_3N_4O$

70	2-Phenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid (3,3-dimethyl-butyl)-amide		3.60 367 $C_{18}H_{21}F_3N_4O$
71	2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (piperidin-4-ylmethyl)-amide trifluoroacetate		2.46 414 $C_{18}H_{19}^{35}ClF_3N_5O$
72	1-[2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-1-(piperazin-1-yl)-methanone		2.42 386 $C_{16}H_{15}^{35}ClF_3N_5O$
73	2-(3-Fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid [(R)-1-(tetrahydro-furan-2-yl)methyl]-amide		3.10 385 $C_{17}H_{16}F_4N_4O_2$

Table 3

Compounds 74 to 87 were prepared according to the conditions described for table 1, and purified by the method given in column P as follows:

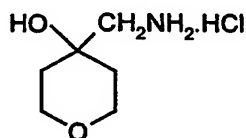
5 Method A: refers to the procedure in part (b) of Example 166.

Method B: Mass-directed autopurification using the procedures detailed at the beginning of the experimental

Method C: Purification using Biotage Chromatography over Merck 9385 Silica Gel (25g) eluting with 1-2% methanol in dichloromethane.

10

Intermediate A: 4-Aminomethyltetrahydropyran-4-ol hydrochloride



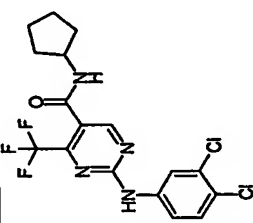
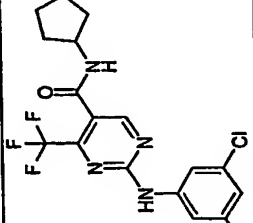
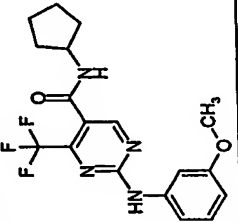
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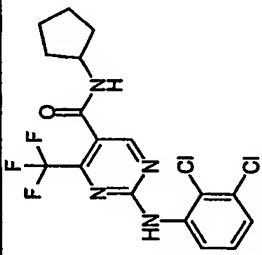
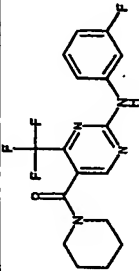
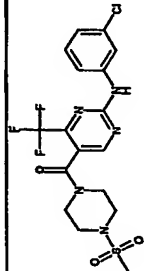
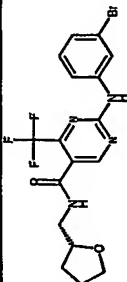
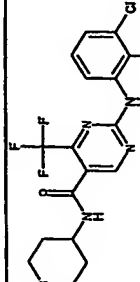
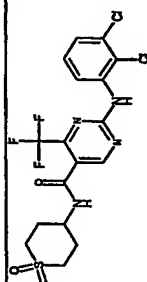
To a solution of 1.0M lithium aluminium hydride in tetrahydrofuran (20 ml) was added under a nitrogen atmosphere a solution of 4-hydroxytetra-hydropyran-4-carbonitrile (0.50 g, prepared as described in Eiden et al., Arch. Pharm., 320, 348, (1987)) in tetrahydrofuran (2 ml) and the solution stirred at reflux for 6 hours. Water (1 ml) and 2N sodium hydroxide solution (1 ml) were added cautiously and the resultant solid filtered and washed with ether. The filtrate was dried (MgSO₄), evaporated and the residue dissolved in ethanol (3 ml) and concentrated hydrochloric acid (0.5 ml) added. Solvent was removed under reduced pressure and the resultant solid washed with ether and dried in vacuo at 40°C to afford the title compound (234 mg).

20

NMR (DMSO-d₆) 1.45-1.6 (4H, m), 2.78 (2H, q), 3.61 (4H, m). 5.07 (1H, br s), 7.89 (3H, br s).

25

Ex	1	2	3 - Product		P	LC/MS 1 Retention time (min) 2 MH ⁺ 3 Formula
74	3,4-Dichloroaniline (Lancaster)	Cyclopentylamine (Aldrich)	3,4-Dichlorophenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylamide		A	3.53 419 C ₁₇ H ₁₅ ³⁵ Cl ₂ F ₃ N ₄ O
75	3,5-Dichloroaniline (Lancaster)	Cyclopentylamine (Aldrich)	3,5-Dichlorophenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylamide		A	3.60 419 C ₁₇ H ₁₅ ³⁵ Cl ₂ F ₃ N ₄ O
76	3-Methoxyaniline (Lancaster)	Cyclopentylamine (Aldrich)	3-Methoxyphenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylamide		A	3.08 381 C ₁₈ H ₁₉ F ₃ N ₄ O ₂

77	2,3-Dichloroaniline (Lancaster)	Cyclopentylamine (Aldrich)	2,3-Dichlorophenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylamide		A	3.60 419 $C_{17}H_{15}^{35}Cl_2$ F_3N_4O
78	3-fluoroaniline (Lancaster)	Piperidine (Aldrich)	1-[2-(3-fluorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-1-piperidin-1-yl-methanone		A	3.39 369 $C_{17}H_{16}N_4F_4O$
79	3-chloroaniline (Lancaster)	1-methanesulfonyl-piperazine (US 5081147)	1-[2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-1-(4-methanesulfonyl-piperazin-1-yl)-methanone		A	3.21 464 $C_{17}H_{17}Cl^{35}F_3N$ $_5O_3S$
80	3-bromoaniline (Lancaster)	R-1-(tetrahydrofuran-2-yl)methylamine (Lancaster)	2-(3-bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid [R-1-(tetrahydrofuran-2-yl)methyl]-amide		A	3.29 447 $C_{17}H_{16}^{81}Br$ $F_3N_4O_2$
81	2,3-dichloroaniline	tetrahydro-thiopyran-4-ylamine JOC 46(22), 4376-83 1981	2-(2,3-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-thiopyran-4-yl)-amide		C	3.74 451 $C_{17}H_{15}^{35}Cl_2F_3$ N_4OS
82	2,3-dichloroaniline	(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)amine	2-(2,3-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (1,1-dioxo-tetrahydro-		C	3.29 483 $C_{17}H_{15}$

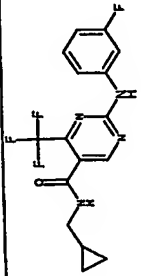
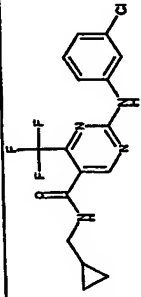
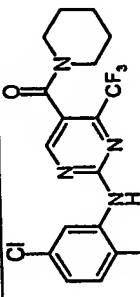
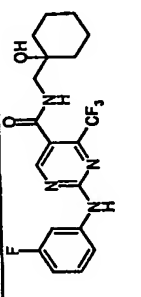
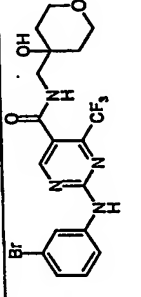
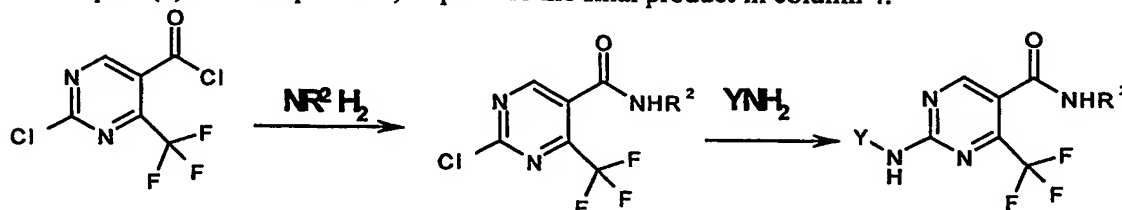
		hydrochloride WO 0218380	2H-thiopyran-4-yl)-amide			³⁵ Cl ₂ F ₃ N ₄ O ₃ S
83	3-fluoroaniline (Lancaster)	cyclopropylmethylamine (Lancaster)	2-(3-Fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (cyclopropylmethyl)-amide		A	3.32 355 C ₁₆ H ₁₄ F ₄ N ₄ O
84	3-chloroaniline (Lancaster)	cyclopropylmethylamine (Lancaster)	2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (cyclopropylmethyl)-amide		B	3.46 371 C ₁₆ H ₁₄ ³⁵ ClF ₃ N ₄ O
85	2,5-Dichloro-aniline (ex Lancaster)	Morpholine (ex Aldrich)	1-[2-(2,5-Dichloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-1-piperidin-1-yl-methanone		A	3.64 419 C ₁₇ H ₁₅ ³⁵ Cl ₂ F ₃ N ₄ O
86	3-Fluoro-aniline (ex Lancaster)	1-Aminomethyl-1-cyclohexanol hydrochloride (ex Aldrich)	2-(3-Fluorophenyl-amino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (1-hydroxycyclohexyl-methyl)-amide		A	3.25 411 C ₁₉ H ₂₀ F ₄ N ₄ O ₂
87	3-Bromo-aniline (ex Lancaster)	4-Aminomethyl-tetrahydro-4H-pyran-4-ol hydrochloride (Intermediate A)	2-(3-Bromophenyl-amino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (1-hydroxytetrahydropyran-4-ylmethyl)amide		A	3.05 473 C ₁₈ H ₁₈ ⁷⁹ BrF ₃ N 4O ₃

Table 4

- In the following table 4, column 2 gives precursors R^2NH_2 that were reacted with 2-chloro-4-(trifluoromethyl)pyrimidine-5-carbonyl chloride in a manner similar to that in part (a) of Example 166 . The resultant product was reacted with the precursor YNH_2 of column 3 in a manner similar to that in part (b) of Example 166 , to provide the final product in column 4.



- Preparation Method A: refers to the procedure give in part (b) of Example 166.
- Preparation Method B: This is exemplified by the by Example 109, 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)amide (50 mg) and 2-chloro-2-cyanoaniline (118mg) were irradiated in a microwave apparatus (the model used was the 'Creator', supplied by 'Personal Chemistry', operating at 300 Watts), at 190°C for 30 min. For examples using this method, the equivalents of substituted aniline YNH_2 used, and duration of irradiation follow in brackets after the method B.

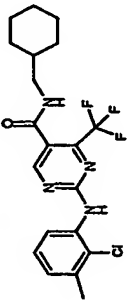
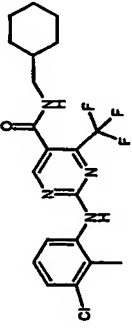
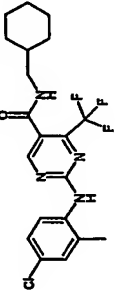
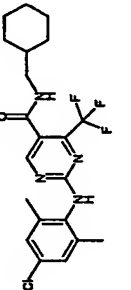
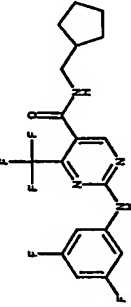
The column entitled "Prep" refers to the preparation method used.

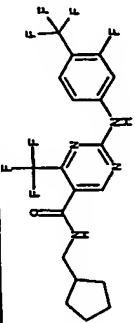
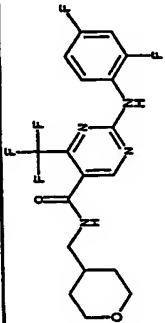
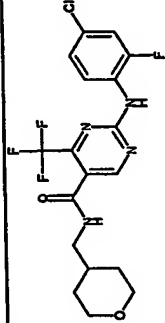
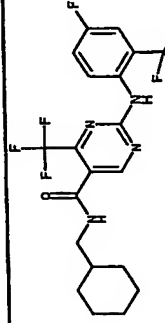
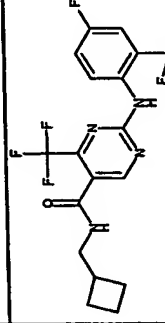
- The product was then purified according to on of the following methods described below. The column entitled "Pure" refers to the purification method used

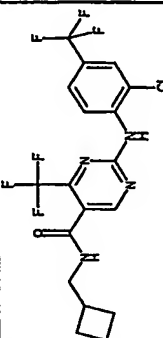
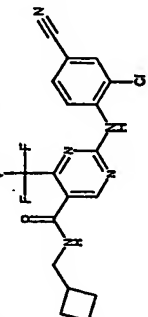
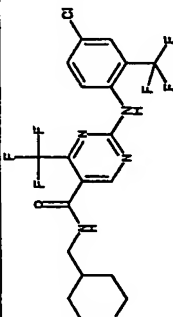
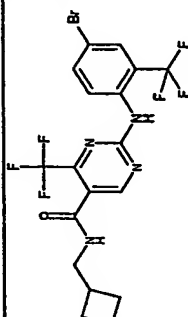
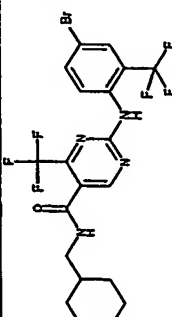
- Purification method A: refers to the procedure give in part (b) of Example 166 .
- Purification method B: mass directed autopurification using the procedures detailed at the beginning of the experimental.
- Purification method C: The reaction was worked up as for part (b) of Example 166, and the crude product further purified by Biotage chromatography over Merck 9385 silica gel, eluting with isohexane/ethyl acetate.

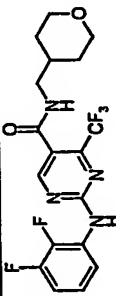
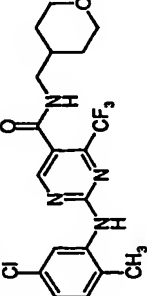
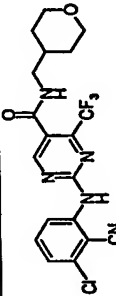
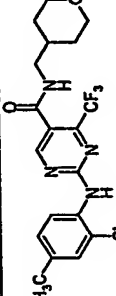
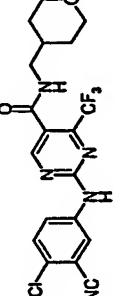
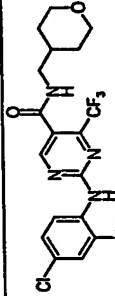
Table 4

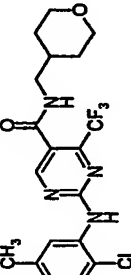
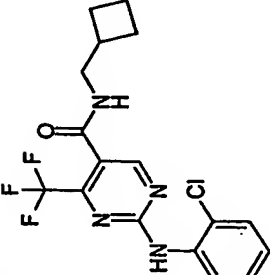
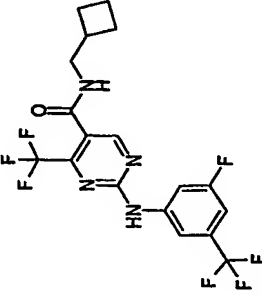
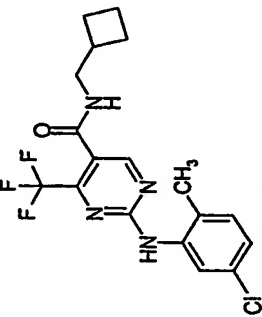
	NR ² H ₂	YNH ₂	Compound	Prep	Pur e	Structure	LCMS 1 Retention time 2 MH ⁺ 3 Formula consistent with MH ⁺
88	Cyclohexanemethanamine (Aldrich)	3,5-Bis-trifluoromethylphenylamine (Aldrich)	2-(3,5-Bis-trifluoromethylphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide	A	B		4.09 515 C ₂₁ H ₁₉ F ₉ N ₄ O
89	Cyclohexanemethanamine	5-Amino-isophthalonitrile	2-(3,5-Dicyano-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide	A	B		3.59 429 C ₂₁ H ₁₉ F ₃ N ₆ O
90	Cyclohexanemethanamine	3-Fluoro-5-trifluoromethylphenylamine (Supplier Apollo)	2-(3-Fluoro-5-trifluoromethylphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide	A	B		3.96 465 C ₂₀ H ₁₉ F ₇ N ₄ O
91	Cyclohexanemethanamine	3-Bromo-5-trifluoromethylphenylamine (Supplier Avacado)	2-(3-Bromo-5-trifluoromethylphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide	A	B		4.13 524 C ₂₀ H ₁₉ ⁷⁹ BrF ₆ N ₄ O

92	Cyclohexanemethanamine	2-Chloro-3-methyl-phenylamine (WO 97/41846 - hydrogenate 2-chloro-3-nitrotoluene.)	2-(2-Chloro-3-methyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide	A	B		3.82 427 $C_{20}H_{22}^{35}ClF_3N_4O$
93	Cyclohexanemethanamine	3-Chloro-2-methyl-phenylamine (Supplier Aldrich)	2-(3-Chloro-2-methyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide	A	B		3.76 427 $C_{20}H_{22}^{35}ClF_3N_4O$
94	Cyclohexanemethanamine	4-Chloro-2-methyl-phenylamine (Supplier Aldrich)	2-(4-Chloro-2-methyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide	A	B		3.77 427 $C_{20}H_{22}^{35}ClF_3N_4O$
95	Cyclohexanemethanamine	4-Chloro-2,6-dimethyl-phenylamine (Supplier Davos)	2-(4-Chloro-2,6-dimethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide	A	B		3.79 441 $C_{21}H_{24}^{35}ClF_3N_4O$
96	Cyclopentane methanamine	3,5-difluoroaniline (Aldrich)	2-(3,5-Difluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide	A	C		3.70 401 $C_{18}H_{17}F_5N_4O$

97	Cyclopentanemethanamine	3-Fluoro-4-(trifluoromethyl)aniline (Fluorochem)	2-(4-Trifluoromethyl-3-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethylamide	A	B		3.86 451 $C_{19}H_{17}F_7N_4O$
98	4-Aminomethyltetrahydropyran (CombiBlocks)	2,4-Difluoroaniline (Lancaster)	2-(2,4-Difluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)amide	A	A		3.03 417 $C_{18}H_{17}F_5N_4O_2$
99	4-Aminomethyltetrahydropyran (CombiBlocks)	2-Fluoro-4-chloroaniline (Lancaster)	2-(2-Fluoro-4-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)amide	A	A		3.23 433 $C_{18}H_{17}^{35}ClF_4N_4O_2$
100	Cyclohexanemethanamine (Lancaster)	2-Trifluoromethyl-4-fluoroaniline (Lancaster)	2-(2-Trifluoromethyl-4-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethylamide	A	B		3.69 465 $C_{20}H_{19}F_7N_4O$
101	Cyclobutanemethanamine	2-Trifluoromethyl-4-fluoroaniline (Lancaster)	2-(2-Trifluoromethyl-4-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethylamide	A	B		3.49 437 $C_{18}H_{13}F_7N_4O$

102	Cyclobutanemethanamine	2-Chloro-4-trifluoromethylaniline (Lancaster)	2-(2-Chloro-4-trifluoromethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethylamide	A	B	 3.79 453 $C_{18}H_{15}^{35}ClF_6N_4O$
103	Cyclobutanemethanamine	2-Chloro-4-cyanoaniline (Lancaster)	2-(2-Chloro-4-cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethylamide	B	C	 3.47 410 $C_{18}H_{15}^{35}ClF_3N_5O$
104	4-Aminomethyltetrahydropyran (CombiBlocks)	2-Trifluoromethyl-4-chloroaniline (Lancaster)	2-(2-Trifluoromethyl-4-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide	A	A	 3.34 483 $C_{19}H_{17}^{35}ClF_6N_4O_2$
105	Cyclobutylmethylamine	2-Trifluoromethyl-4-bromoaniline (Lancaster)	2-(2-Trifluoromethyl-4-bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethylamide	B (5 equiv, 45 min)	B	 3.71 499 $C_{18}H_{15}^{81}BrF_6N_4O$
106	Cyclohexylmethylamine	2-Trifluoromethyl-4-bromoaniline (Lancaster)	2-(2-Trifluoromethyl-4-bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethylamide	B (2.5 equiv, 45 min)	B	 3.89 527 $C_{20}H_{19}^{81}BrF_6N_4O$

107	4-Aminomethyl-tetrahydropyran (ex Combi Blocks)	2,3-Difluoro-aniline (ex Aldrich)	2-(2,3-Difluoro-phenylamino)-4-tri-fluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide	A	B		3.64 417 $C_{18}H_{17}F_5N_4O_2$
108	4-Aminomethyl-tetrahydropyran (ex Combi Blocks)	5-Chloro-2-methylaniline (ex Aldrich)	2-(5-Chloro-2-methyl-phenylamino)-4-tri-fluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide	A	B		3.64 429 $C_{19}H_{20}^{35}ClF_3N_4O_2$
109	4-Aminomethyl-tetrahydropyran (ex Combi Blocks)	3-Chloro-2-cyanoaniline (ex Lancaster)	2-(3-Chloro-2-cyano-phenylamino)-4-tri-fluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide	B (5 equiv, 30 min)	B		3.64 440 $C_{19}H_{17}^{35}ClF_3N_5O_2$
110	4-Aminomethyl-tetrahydropyran (ex Combi Blocks)	2-Chloro-4-methylaniline	2-(2-Chloro-4-methyl-phenylamino)-4-tri-fluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide	A	B		3.27 429 $C_{19}H_{20}^{35}ClF_3N_4O_2$
111	4-Aminomethyl-tetrahydropyran (ex Combi Blocks)	4-Chloro-3-cyanoaniline	2-(4-Chloro-3-cyano-phenylamino)-4-tri-fluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide	A	B		3.22 440 $C_{19}H_{17}^{35}ClF_3N_5O_2$
112	4-Aminomethyl-tetrahydropyran (ex Combi Blocks)	4-Chloro-2-methylaniline (ex Aldrich)	2-(4-Chloro-2-methyl-phenylamino)-4-tri-fluoromethyl-pyrimidin-5-carboxylic acid	A	B		3.23 429 $C_{19}H_{20}^{35}ClF_3N_4O_2$

113	4-Aminomethyl-tetrahydropyran (ex Combi Blocks)	2-Chloro-5-methylaniline (ex Aldrich)	(tetrahydropyran-4-ylmethyl)-amide 2-(2-Chloro-5-methylphenylamino)-4-trifluoromethylpyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide	A	B		3.28 429 $C_{19}H_{20}^{35}ClF_3N_4O_2$
257	(Cyclobutylmethyl)amine	2-Chloroaniline	2-(2-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (cyclobutylmethyl)amide	C (5 equiva lents, 2 x 30 min)	B		3.52 385 $C_{17}H_{16}^{35}ClF_3N_4O$
258	(Cyclobutylmethyl)amine	3-Fluoro-5-trifluoromethylaniline	2-(3-Fluoro-5-trifluoromethylphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (cyclobutylmethyl)amide	C (5 equiva lents, 2 x 30 min)	B		3.80 437 $C_{18}H_{15}F_7N_4O$
259	(Cyclobutylmethyl)amine	5-Chloro-2-methylaniline	2-(5-Chloro-2-methylphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (cyclobutylmethyl)amide	C (5 equiva lents, 2 x 30 min)	B		3.61 399 $C_{18}H_{18}^{35}ClF_3N_4O$

****In Example 103 – Preparation Method B (5 equiv, 15 min) N.B. Reaction mixture also contained 0.5 ml MeCN and purification method C The product was purified by trituration with isohexane after this.**

5 Method C - As for method B, but the solvent used was 1,4-dioxan not MeCN

Table 5

Compounds 114 to 145 and 260 were prepared as set out for table 2 and purified as follows:

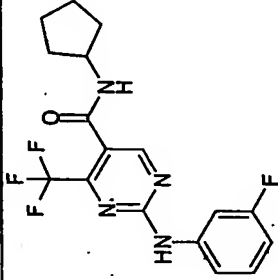
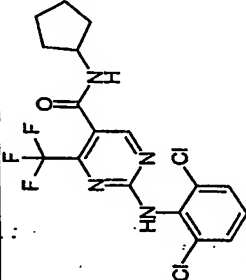
Purification Method A: as for reference example 1c,

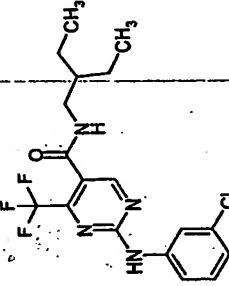
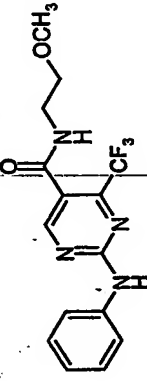
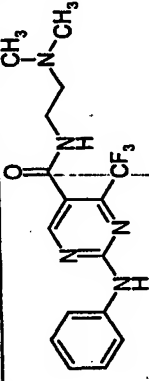
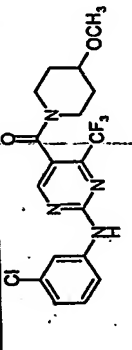
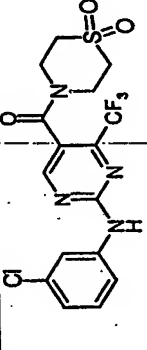
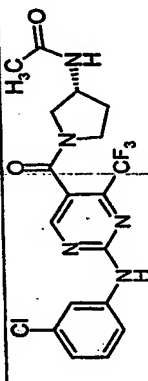
Purification Method B: The reaction was worked up as in example 1c, and the product purified by Biotage chromatography using the following solvent systems:

Sol 1 ethyl acetate

Sol 2 1% methanol in dichloromethane

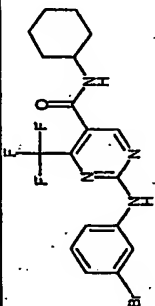
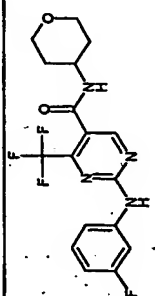
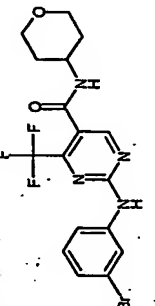
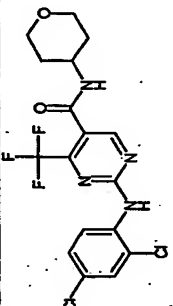
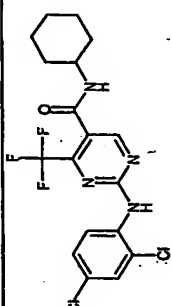
Sol 3 2% methanol in dichloromethane

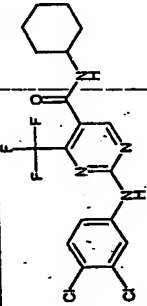
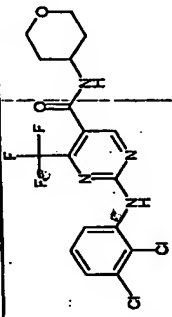
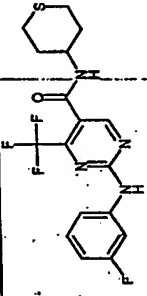
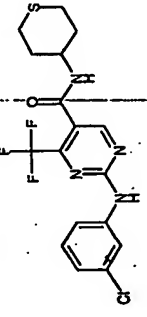
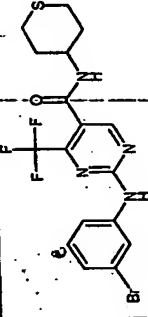
	Compound Name	Structure	Purification method	Mass spec details 1 Retention Time 2 MH ⁺ 3 Formula consistent with MH ⁺
114	3-Fluorophenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentyl-amide		A	3.23 369 C ₁₇ H ₁₆ F ₄ N ₄ O
115	2,6-Dichlorophenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylamide		A	3.17 419 C ₁₇ H ₁₅ ³⁵ Cl ₂ F ₃ N ₄ O

116	3-Chlorophenylamino-4-trifluoromethylpyrimidine-5-carboxylic acid (2-ethylbutyl)-amide		A	3.79 401 $C_{18}H_{20}^{35}ClF_3N_4O$
117	2-Phenylamino-4-trifluoromethyl-pyrimidin-5-carboxylic acid (2-methoxy-ethyl)-amide		A	2.98 339 $C_{15}H_{15}F_3N_4O_2$
118	2-Phenylamino-4-trifluoromethyl-pyrimidin-5-carboxylic acid [2-(dimethyl-amino)ethyl]-amide		A	2.32 354 $C_{18}H_{18}F_3N_5O$
119	1-[2-(3-Chlorophenyl-amino)-4-trifluoromethylpyrimidin-5-yl]-1-(4-methoxypiperin-1-yl)-methanone		A	3.33 415 $C_{18}H_{18}^{35}ClF_3N_4O_2$
120	1-[2-(3-Chlorophenyl-amino)-4-trifluoromethylpyrimidin-5-yl]-1-(1,1-dioxothiomorpholin-4yl)-methanone		A	3.16 435 $C_{16}H_{14}^{35}ClF_3N_4O_3S$
121	N-(R)-1-{1-[2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanoyl}-pyrrolidin-3-yl)-acetamide		A	2.91 428 $C_{18}H_{17}^{35}ClF_3N_5O_2$

122	N-((S)-1-{1-[2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanoyl}-pyrrolidin-3-yl)-acetamide		A	2.91 428 $C_{18}H_{17}^{35}ClF_3N_5O_2$
123	1-{1-[2-(3-Chloro-phenylamino)-4-tri-fluoromethyl-pyrimidin-5-yl]-methanoyl}-piperidine-4-carboxylic acid methylamide		C Sol 1	2.98 442 $C_{19}H_{19}^{35}ClF_3N_5O_2$
124	2-(3-Chlorophenyl-amino)-4-trifluoro-methylpyrimidin-5-carboxylic acid (1-hydroxytetrahydropyran-4-ylmethyl)amide		A	3.00 429 $C_{18}H_{18}^{35}ClF_3N_4O_3$
125	2-(3-Fluorophenyl-amino)-4-trifluoro-methylpyrimidin-5-carboxylic acid (1-hydroxytetrahydropyran-4-ylmethyl)amide		A	2.86 413 $C_{18}H_{18}F_4N_4O_3$
126	1-[2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-(4-methylpiperazin-1-yl)-methanone		A	2.53 400 $C_{17}H_{17}^{35}ClF_3N_5O$
127	2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (2-methoxy-ethyl)-amide		A	3.23 375 $C_{15}H_{14}^{35}ClF_3N_4O_2$

128	2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (2-dimethylamino-ethyl)-amide		A	2.51 388 $C_{16}H_{17}^{35}ClF_3N_5O$
129	2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid [R-1-(tetrahydrofuran-2-yl)methyl]-amide		A	3.25 401 $C_{17}H_{16}^{35}ClF_3N_4O_2$
130	2-(Phenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)amide		A	3.01 381 $C_{18}H_{19}F_3N_4O_2$
131	2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylamide		C Sol 2	3.74 433 $C_{18}H_{17}^{35}Cl_2F_3N_4O$
132	2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylamide		A	3.56 383 $C_{18}H_{18}F_4N_4O$

133	2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylamide		A	3.74 445 $C_{18}H_{18}^{81}BrF_3N_4O$
134	2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-yl)-amide		A	3.06 385 $C_{17}H_{16}F_4N_4O_2$
135	2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-yl)-amide		A	3.26 447 $C_{17}H_{16}^{81}BrF_3N_4O_2$
136	2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-yl)-amide		A	3.33 435 $C_{17}H_{15}^{35}Cl_2F_3N_4O_2$
137	2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylamide		A	3.79 433 $C_{18}H_{17}^{35}Cl_2F_3N_4O$

138	2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylamide		A	3.90 433 $C_{18}H_{17}^{35}Cl_2F_3N_4O$
139	2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-yl)-amide		A	3.26 435 $C_{17}H_{15}^{35}Cl_2F_3N_4O_2$
140	2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-thiopyran-4-yl)-amide		C Sol 2	3.37 401 $C_{17}H_{16}F_4N_4OS$
141	2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-thiopyran-4-yl)-amide		C Sol 2	3.51 417 $C_{17}H_{16}^{35}ClF_3N_4OS$
142	2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-thiopyran-4-yl)-amide		C Sol 2	3.55 463 $C_{17}H_{16}^8BrF_3N_4OS$

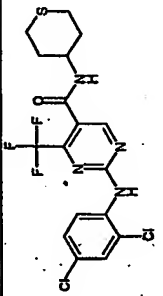
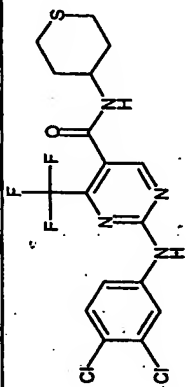
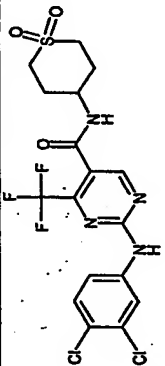
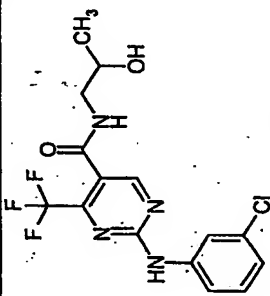
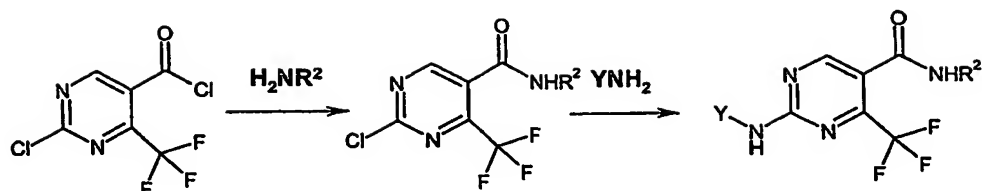
143	2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-thiopyran-4-yl)-amide		C Sol 2	3.61 451 $C_{17}H_{15}^{35}Cl_2F_3N_4O_2S$
144	2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-thiopyran-4-yl)-amide		C Sol 2	3.72 451 $C_{17}H_{15}^{35}Cl_2F_3N_4OS$
145	2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (1,1-dioxo-hexahydro-1 β -thiopyran-4-yl)-amide		C Sol 3	3.32 483 $C_{17}H_{15}^{35}Cl_2F_3N_4O_3S$
260	3-Chlorophenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid 2-(hydroxypropyl)amide		A	3.09 375 $C_{15}H_{14}^{35}ClF_3N_4O_2$

Table 6



- 5 Preparation Method A: refers to the procedure give in part (b) of Example 166.
- Preparation Method B: Exemplified by Example 154: A mixture of 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg), 3,5-dicyanoaniline (69mg), and acetonitrile (0.5ml) was irradiated in a microwave apparatus (the model used was the 'Creator', supplied by 'Personal Chemistry', operating at 300 Watts), at 180°C for 60 min. The
- 10 temperature, duration of irradiation, and number of equivalents of the substituted-aniline used are given after the method in the table.
- Preparation Method C: exemplified by Example 162: A mixture of 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (80 mg) and 4-fluoro-2-(trifluoromethyl)aniline (111mg) was irradiated in microwave apparatus (the model used was the
- 15 'Creator', supplied by 'Personal Chemistry', operating at 300 Watts), at 190°C for 45 min.

Purification was carried out as detailed in the table to give the product.

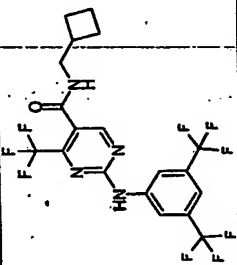
- Purification Method A: refers to the procedure give in part (b) of Example 166.
- 20 Purification Method B: mass directed autopurification using the procedures detailed at the beginning of the experimental.
- Purification Method C: The reaction was worked up as for part (b) of Example 166, and the crude product further purified by Biotage chromatography over Merck 9385 silica gel, eluting with isohexane/ethyl acetate (7:3).

Table 6

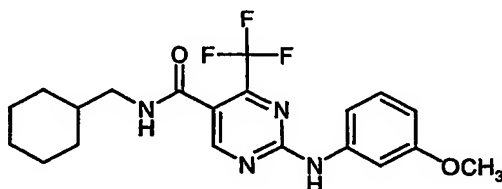
Ex.	Compound Name	Structure	Preparation Method	Purification method	LCMS 1 Retention time (min) 2 MH ⁺ 3 Consistent Formula
146	2-(3-Methoxy-5-trifluoromethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (cyclohexylmethyl)-amide		A	B	3.91 477 C ₂₁ H ₂₂ F ₆ N ₄ O ₂
147	2-(4-Chloro-3-methyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	B	3.96 427 C ₂₀ H ₂₂ ³⁵ ClF ₃ N ₄ O
148	2-(3-Chloro-4-methyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid N-cyclohexylmethyl-amide		A	B	3.92 427 C ₂₀ H ₂₂ ³⁵ ClF ₃ N ₄ O
149	2-(4-Chloro-3-cyano-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	B	3.76 438 C ₂₀ H ₁₉ ³⁵ ClF ₃ N ₅ O
150	2-(2-Chloro-5-methyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	B	3.82 427 C ₂₀ H ₂₂ ³⁵ ClF ₃ N ₄ O
151	2(3-Chloro-2,6-dimethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	B	3.76 441 C ₂₁ H ₂₄ ³⁵ ClF ₃ N ₄ O

152	2-(3-Chloro-4-tri-fluoromethoxyphenyl-amino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	A	4.00 497 C ₂₀ H ₁₉ ³⁵ ClF ₆ N ₄ O ₂
153	2-(3-Fluoro-4-tri-fluoromethylphenyl-amino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	C	3.89 465 C ₂₀ H ₁₉ F ₇ N ₄ O
154	2-(3,5-Dicyano-phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)amide		B (180°, 60 mins, 3 equiv)	B	3.01 431 C ₂₀ H ₁₇ F ₃ N ₆ O ₂
155	2-(3-Chloro-2,6-di-methylphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide		A	B	3.22 443 C ₂₀ H ₂₂ ³⁵ ClF ₃ N ₄ O ₂
156	2-(2-Chloro-6-methyl-phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide		B (180°, 60 mins, 5 equiv)	B	3.05 429 C ₁₉ H ₂₀ ³⁵ ClF ₃ N ₄ O ₂
157	2-(2-Chloro-3-methyl-phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide		A	B	3.27 429 C ₁₉ H ₂₀ ³⁵ ClF ₃ N ₄ O ₂

158	2-(4-Chloro-2,6-dimethylphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide		A	B	3.26 443 $C_{20}H_{22}^{35}ClF_3N_4O_2$
159	2-(5-Chloro-2-sulfamoylphenyl-amino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide		B (180°, 60 mins, 5 equiv)	B	3.08 494 $C_{18}H_{19}^{35}ClF_3N_5O_4S$
160	2-(2-Fluoro-4-trifluoromethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide		A	A	3.67 437 $C_{18}H_{15}F_7N_4O$
161	2-(2-Chloro-4-trifluoromethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	B	3.97 481 $C_{20}H_{19}^{35}ClF_6N_4O$
162	2-(2-Trifluoromethyl-4-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)amide		C	B	3.16 467 $C_{19}H_{17}N_4O_2F_7$
261	2-(2-Fluoro-4-trifluoromethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)amide		B 180°, 2x42min, 5 equivalents	B	3.37 467 $C_{19}H_{17}F_7N_4O_2$

262	2-(3,5-Bistrifluoromethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (cyclobutylmethyl)amide		B 180°, 30 min, 5 equivalents	B	Molecular ion observed [M-H] ⁻ 485 consistent with molecular formula C ₁₉ H ₁₅ F ₉ N ₄ O
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Example 163 2-(3-Methoxyphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide

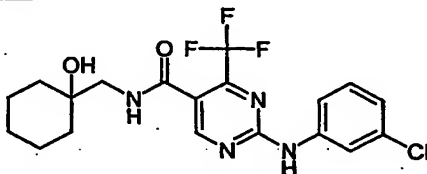


- 5 In a manner similar to Reference Example 1(c) 2-(3-methoxyphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclohexanemethanamine (16 μ l, ex Lancaster) afforded the title compound (28 mg).

NMR (DMSO- d_6) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.55-1.75 (5H, m), 3.06 (2H, t), 3.74 (3H, s), 6.63 (1H, d), 7.2-7.3 (2H, m), 7.54 (1H, s), 8.57 (1H, t), 8.74 (1H, s), 10.35 (1H, s).

LC/MS, $t = 3.57$ min, Molecular ion observed $[MH]^+ = 409$ consistent with the molecular formula $C_{20}H_{23}F_3N_4O_2$.

Example 164: 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (1-hydroxycyclohexylmethyl)-amide

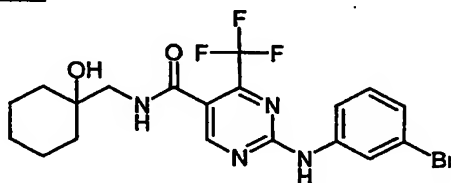


In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and 1-aminomethyl-1-cyclohexanol hydrochloride (20 mg, ex Aldrich) afforded the title compound (29 mg).

NMR (DMSO- d_6) δ 1.3 (1H, m), 1.4-1.5 (7H, m), 1.6 (2H, m), 3.28 (2H, d), 4.34 (1H, s), 7.16 (1H, d), 7.43 (1H, t), 7.73 (1H, d), 8.04 (1H, t), 8.51 (1H, t), 8.91 (1H, s), 10.65 (1H, s).

LC/MS, $t = 3.39$ min, Molecular ion observed $[M-H]^- = 427$ consistent with the molecular formula $C_{19}H_{20}^{35}ClF_3N_4O_2$.

Example 165: 2-(3-Bromophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (1-hydroxycyclohexylmethyl)-amide



In a manner similar to Reference Example 1(c) 2-(3-bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (36.5 mg) and 1-aminomethyl-1-cyclohexanol hydrochloride (20 mg, ex Aldrich) afforded the title compound (28 mg).

NMR (DMSO- d_6) δ 1.25 (1H, m), 1.35-1.45 (7H, m), 1.6 (2H, m), 3.23 (2H, d), 4.28 (1H, s), 7.23 (1H, d), 7.31 (1H, t), 7.71 (1H, d), 8.12 (1H, s), 8.45 (1H, t), 8.85 (1H, s), 10.55 (1H, s).

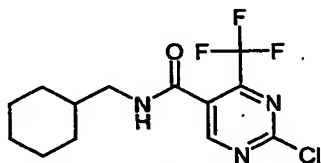
LC/MS, $t = 3.43$ min, Molecular ion observed $[M-H]^- = 471$ consistent with the molecular formula $C_{19}H_{20}^{79}BrF_3N_4O_2$.

Example 166: 2-(3-Chloro-4-fluorophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide

(a). To a solution of 2-chloro-4-trifluoromethyl-pyrimidin-5-carbonyl chloride (750 mg, ex Maybridge) in dichloromethane (15 ml) at -40° was added dropwise over 30 minutes a solution of cyclohexanemethanamine (0.35 ml, ex Lancaster) and triethylamine (0.41 ml) in dichloromethane (15 ml). Dichloromethane was removed under reduced pressure and ethyl acetate (20 ml) added. The solution was washed sequentially with water, 5% sodium bicarbonate solution and water, dried ($MgSO_4$), evaporated and triturated with ether:hexane to afford 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide (666 mg).

NMR (DMSO- d_6) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.55-1.75 (5H, m), 3.12 (2H, t), 8.75 (1H, t), 9.18 (1H, s).

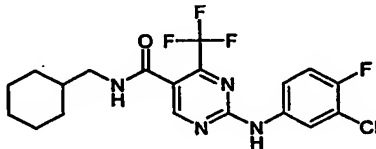
LC/MS, $t = 3.31$ min, Molecular ion observed $[MH]^+ = 322$ consistent with the molecular formula $C_{13}H_{15}^{35}ClF_3N_3O$.



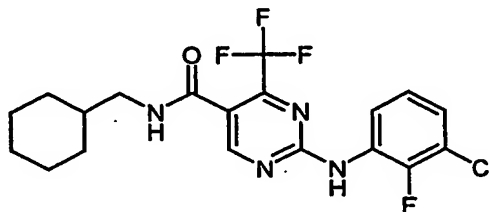
(b). To a solution of 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide (100 mg) in 1,4-dioxan (1 ml) was added 3-chloro-4-fluoroaniline (228 mg, ex Lancaster) and the solution stirred at reflux for 4 hours. Dioxan was removed under reduced pressure and ethyl acetate (5 ml) added. The solution was washed sequentially with 2N hydrochloric acid (2 x 3 ml) and water (3 x 3 ml), dried ($MgSO_4$), evaporated and triturated with isohexane to afford the title compound (107 mg).

NMR (DMSO- d_6) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.45 (1H, m), 1.6-1.75 (5H, m), 3.06 (2H, t), 7.25 (1H, t), 7.43 (1H, t), 7.56 (1H, t), 8.56 (1H, t), 8.69 (1H, s), 10.20 (1H, s).

LC/MS, $t = 3.81$ min, Molecular ion observed $[MH]^+ = 431$ consistent with the molecular formula $C_{19}H_{19}^{35}ClF_4N_4O$.



Example 167: 2-(3-Chloro-2-fluorophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide

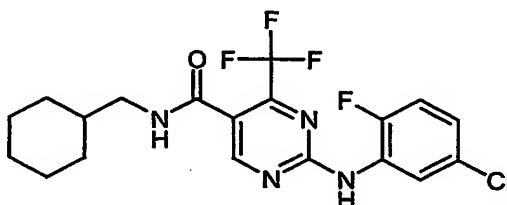


In a manner similar to Example 166(b), 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide (100 mg) and 3-chloro-2-fluoroaniline (230 mg, ex Acros) afforded the title compound (101 mg).

5 NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.6-1.8 (5H, m), 3.08 (2H, t), 7.43 (1H, t), 7.67 (1H, m), 8.07 (1H, d), 8.58 (1H, t), 8.80 (1H, s), 10.60 (1H, s).

LC/MS, $t = 3.71$ min, Molecular ion observed $[MH^+] = 431$ consistent with the molecular formula $C_{19}H_{19}^{35}ClF_4N_4O$.

10 Example 168: 2-(5-Chloro-2-fluorophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide

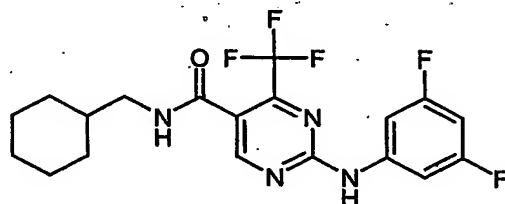


In a manner similar to Example 166(b), 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide (100 mg) and 5-chloro-2-fluoroaniline (230 mg, ex Avocado) afforded the title compound (116 mg).

15 NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.6-1.75 (5H, m), 3.07 (2H, t), 7.29 (1H, m), 7.36 (1H, t), 7.77 (1H, d of d), 8.57 (1H, t), 8.72 (1H, s), 10.15 (1H, s).

LC/MS, $t = 3.73$ min, Molecular ion observed $[MH^+] = 431$ consistent with the molecular formula $C_{19}H_{19}^{35}ClF_4N_4O$.

20 Example 169: 2-(3,5-Difluorophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide



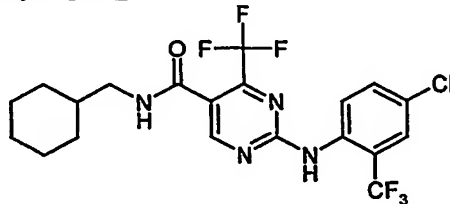
In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide (100 mg) and 3,5-difluoroaniline (200 mg, ex Lancaster) afforded the title compound (110 mg).

25 NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.6-1.75 (5H, m), 3.09 (2H, t), 6.89 (1H, t), 7.54 (2H, d), 8.60 (1H, t), 8.85 (1H, s), 10.80 (1H, s).

LC/MS, $t = 3.74$ min, Molecular ion observed $[MH^+] = 415$ consistent with the molecular formula $C_{19}H_{19}F_5N_4O$.

30

Example 170: 2-(4-Chloro-2-trifluoromethylphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide

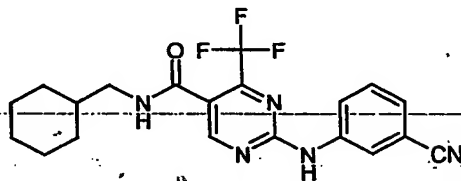


In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide (80 mg) and 4-chloro-2-trifluoromethylaniline (107 mg, ex Lancaster) afforded, after purification by mass-directed autoprereparation technique, the title compound (6 mg).

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.55-1.75 (5H, m), 3.06 (2H, t), 7.76 (1H, d), 7.88 (1H, d), 7.97 (1H, s), 8.56 (1H, t), 8.70 (1H, s), 10.15 (1H, s).

LC/MS, $t = 3.97$ min, Molecular ion observed $[MH^+] = 481$ consistent with the molecular formula $C_{20}H_{19}^{35}ClF_6N_4O$.

Example 171: 2-(3-Cyanophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide

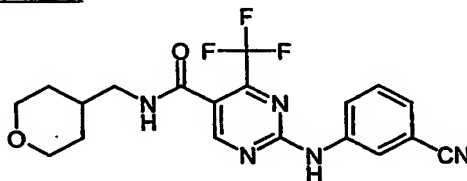


To a solution of 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide (50 mg) in acetonitrile (0.5 ml) was added 3-aminobenzonitrile (92 mg, ex Aldrich) and the solution heated at 200°C under microwave conditions for 45 minutes. Acetonitrile was removed under reduced pressure and ethyl acetate (5 ml) added. The solution was washed sequentially with 2N hydrochloric acid (2 x 3 ml) and water (3 x 3 ml), dried (MgSO₄), evaporated and the residue purified using silica gel chromatography with 1:1 ethyl acetate:isohexane to afford the title compound (37 mg).

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.6-1.8 (5H, m), 3.08 (2H, t), 7.50 (1H, d), 7.57 (1H, t), 8.00 (1H, d), 8.25 (1H, s), 8.59 (1H, t), 8.83 (1H, s), 10.75 (1H, s).

LC/MS, $t = 3.51$ min, Molecular ion observed $[MH^+] = 404$ consistent with the molecular formula $C_{20}H_{20}F_3N_5O$.

Example 172: 2-(3-Cyanophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide

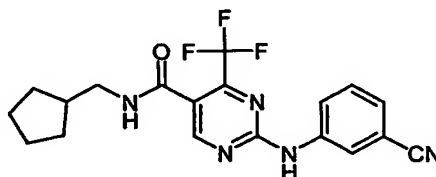


In a manner similar to Reference Example 1(c) 2-(3-cyanophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and 4-aminomethyltetrahydropyran (14 mg, ex Combi Blocks) afforded the title compound (26 mg).

NMR (DMSO-d₆) δ 1.15-1.25 (2H, m), 1.62 (2H, d), 1.74 (1H, m), 3.14 (2H, t), 3.27 (2H, t), 3.86 (2H, d of d), 7.50 (1H, d), 7.57 (1H, t), 8.00 (1H, d), 8.26 (1H, s), 8.65 (1H, t), 8.85 (1H, s), 10.70 (1H, s).

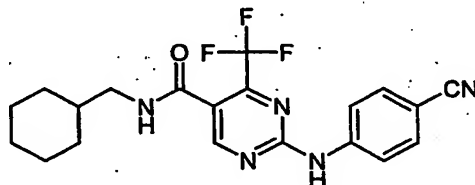
- 5 LC/MS, $t = 2.94$ min, Molecular ion observed $[MH^+] = 406$ consistent with the molecular formula $C_{19}H_{18}F_3N_5O_2$.

Example 173: 2-(3-Cyanophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclopentylmethyl-amide



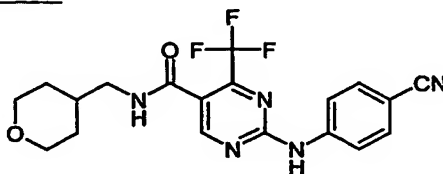
- 10 In a manner similar to Reference Example 1(c) 2-(3-cyanophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclopentanemethanamine hydrochloride (17 mg) afforded the title compound (16 mg).
- NMR (DMSO-d₆) δ 1.20-1.30 (2H, m), 1.45-1.6 (4H, m), 1.65-1.75 (2H, m), 2.08 (1H, quintuplet), 3.19 (2H, t), 7.50 (1H, d), 7.57 (1H, t), 8.00 (1H, d), 8.25 (1H, s), 8.63 (1H, t), 8.82 (1H, s), 10.70 (1H, s).
- 15 LC/MS, $t = 3.42$ min, Molecular ion observed $[MH^+] = 390$ consistent with the molecular formula $C_{19}H_{18}F_3N_5O$.

Example 174: 2-(4-Cyanophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclohexylmethyl-amide



- In a manner similar to Reference Example 1(c) 2-(4-cyanophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclohexanemethanamine (16 μ l, ex Lancaster) afforded the title compound (18 mg).
- 25 NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.6-1.8 (5H, m), 3.08 (2H, t), 7.81 (2H, d), 7.97 (2H, d), 8.61 (1H, t), 8.85 (1H, s), 10.90 (1H, s).
- LC/MS, $t = 3.51$ min, Molecular ion observed $[MH^+] = 404$ consistent with the molecular formula $C_{20}H_{20}F_3N_5O$.

Example 175: 2-(4-Cyanophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)amide

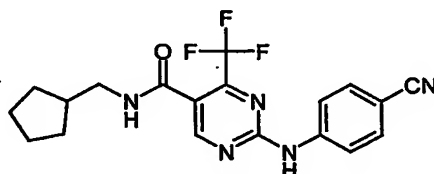


In a manner similar to Reference Example 1(c) 2-(4-cyanophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and 4-aminomethyltetrahydropyran (14 mg, ex Combi Blocks) afforded the title compound (6 mg).

NMR (DMSO-d₆) δ 1.15-1.25 (2H, m), 1.60 (2H, d), 1.75 (1H, m), 3.14 (2H, t), 3.27 (2H, t), 3.86 (2H, d), 7.82 (2H, d), 7.97 (2H, d), 8.67 (1H, t), 8.87 (1H, s), 10.85 (1H, s).

LC/MS, $t = 2.92$ min, Molecular ion observed $[MH^+] = 406$ consistent with the molecular formula $C_{19}H_{18}F_3N_5O_2$.

Example 176: 2-(4-Cyanophenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclopentylmethyl-amide



In a manner similar to Reference Example 1(c) 2-(4-cyanophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclopentanemethanamine hydrochloride (17 mg) afforded the title compound (22.5 mg).

NMR (DMSO-d₆) δ 1.15-1.30 (2H, m), 1.45-1.65 (4H, m), 1.65-1.75 (2H, m), 2.08 (1H, quintuplet), 3.17 (2H, t), 7.82 (2H, d), 7.97 (2H, d), 8.64 (1H, t), 8.84 (1H, s), 10.90 (1H, s).

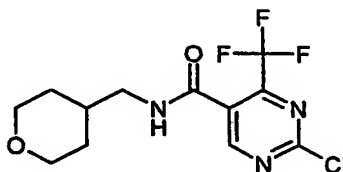
LC/MS, $t = 3.40$ min, Molecular ion observed $[MH^+] = 390$ consistent with the molecular formula $C_{19}H_{18}F_3N_5O$.

Example 177: 2-(3-Methoxy-5-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide

(a). To a solution of 2-chloro-4-trifluoromethyl-pyrimidin-5-carbonyl chloride (1.5 g) in dichloromethane (20 ml) at -2° was added a dropwise a solution of 4-aminomethyltetrahydropyran (0.70 g, ex Combi Blocks) and triethylamine (1.05 ml) in dichloromethane (10 ml) and the solution stirred at 0° for 1 hour. Dichloromethane was removed under reduced pressure and ethyl acetate (30 ml) added. The solution was washed with 2N hydrochloric acid (3 x 20 ml), dried ($MgSO_4$), evaporated and the residue purified using silica gel chromatography with 1:1 ethyl acetate:isohexane to afford 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-yl-methyl)-amide (1.20 g).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.61 (2H, d), 1.74 (1H, m), 3.17 (2H, t), 3.25 (2H, t), 3.86 (2H, d of d), 8.81 (1H, t), 9.20 (1H, s).

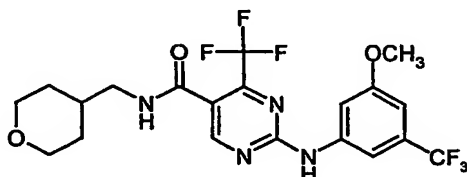
LC/MS, $t = 2.54$ min, Molecular ion observed $[MH^+] = 324$ consistent with the molecular formula $C_{12}H_{13}^{35}ClF_3N_3O_2$.



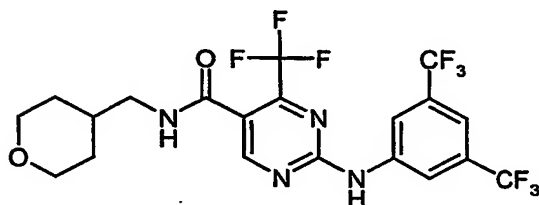
(b). In a manner similar to Example 166(b), 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 3-methoxy-5-(trifluoromethyl)aniline (148 mg, ex Aldrich) afforded after stirring at reflux for 24 hours the title compound (51 mg).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.62 (2H, d), 1.74 (1H, m), 3.13 (2H, t), 3.27 (2H, t), 3.83 (3H, s), 3.86 (2H, d), 6.92 (1H, s), 7.73 (1H, s), 7.80 (1H, s), 8.64 (1H, t), 8.85 (1H, s), 10.65 (1H, s).

LC/MS, $t = 3.38$ min, Molecular ion observed $[MH^+] = 479$ consistent with the molecular formula $C_{20}H_{20}F_6N_4O_3$.



10 Example 178: 2-(3,5-Bis(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide

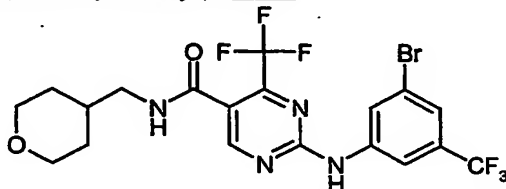


In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 3,5-bis(trifluoromethyl)aniline (177 mg, ex Aldrich) afforded, after stirring at reflux for 80 hours and purification by mass-directed autoprereparation technique, the title compound (24.5 mg).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.62 (2H, d), 1.75 (1H, m), 3.14 (2H, t), 3.28 (2H, t), 3.86 (2H, d), 7.72 (1H, s), 8.49 (2H, s), 8.67 (1H, t), 8.93 (1H, s), 11.05 (1H, s).

LC/MS, $t = 3.62$ min, Molecular ion observed $[MH^+] = 517$ consistent with the molecular formula $C_{20}H_{17}F_9N_4O_2$.

Example 179: 2-(3-Bromo-5-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide

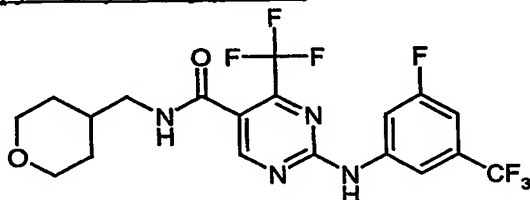


In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 3-bromo-5-(trifluoromethyl)aniline (185 mg, ex Avocado) afforded, after stirring at reflux for 80 hours and purification by mass-directed autoprereparation technique, the title compound (28 mg).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.62 (2H, d), 1.74 (1H, m), 3.14 (2H, t), 3.28 (2H, t), 3.86 (2H, d), 7.60 (1H, s), 8.24 (1H, s), 8.29 (1H, s), 8.66 (1H, t), 8.99 (1H, s), 10.90 (1H, s).

LC/MS, $t = 3.63$ min, Molecular ion observed $[M-H]^- = 527$ consistent with the molecular formula $C_{19}H_{17}^{79}BrF_6N_4O_2$.

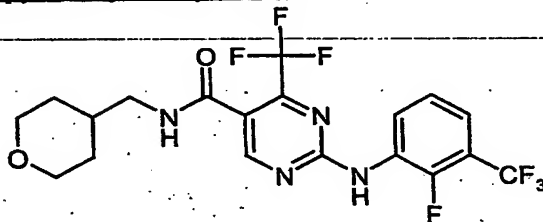
Example 180: 2-(3-Fluoro-5-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 3-fluoro-5-(trifluoromethyl)aniline (138 mg, ex Fluorochem) afforded after stirring at reflux for 24 hours the title compound (44 mg).

- 10 NMR (DMSO- d_6) δ 1.15-1.3 (2H, m), 1.62 (2H, d), 1.75 (1H, m), 3.14 (2H, t), 3.28 (2H, t), 3.86 (2H, d), 7.32 (1H, d), 7.96 (1H, d), 8.06 (1H, s), 8.67 (1H, t), 8.90 (1H, s), 10.90 (1H, s).
LC/MS, $t = 3.45$ min, Molecular ion observed $[MH]^+ = 467$ consistent with the molecular formula $C_{19}H_{17}F_7N_4O_2$.

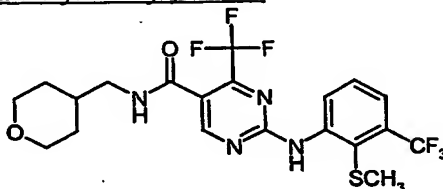
Example 181: 2-(2-Fluoro-3-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 2-fluoro-3-(trifluoromethyl)aniline (138 mg, ex

- 20 Aldrich) afforded, after stirring at reflux for 80 hours and purification by mass-directed autoprereparation technique, the title compound (15 mg).
NMR (DMSO- d_6) δ 1.1-1.25 (2H, m), 1.60 (2H, d), 1.73 (1H, m), 3.11 (2H, t), 3.26 (2H, t), 3.85 (2H, d), 7.43 (1H, t), 7.61 (1H, t), 7.92 (1H, s), 8.63 (1H, t), 8.72 (1H, s), 10.30 (1H, s).
LC/MS, $t = 3.28$ min, Molecular ion observed $[MH]^+ = 467$ consistent with the molecular
25 formula $C_{19}H_{17}F_7N_4O_2$.

Example 182: 2-(2-Methylthio-3-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



- 30 2-Chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg), 2-methylthio-3-(trifluoromethyl)aniline (125 mg, ex Maybridge) and acetonitrile (0.5ml)

were heated at 190° under microwave irradiation for 30 minutes. The solvent was evaporated in vacuo and the residue purified by mass-directed autopreparation technique, to give the title compound (11 mg).

NMR (DMSO-d₆) δ 1.1-1.25 (2H, m), 1.60 (2H, d), 1.73 (1H, m), 2.24 (3H, s), 3.12 (2H, t), 3.26 (2H, t), 3.85 (2H, d), 7.65 (2H, d), 8.11 (1H, t), 8.64 (1H, t), 8.72 (1H, s), 9.81 (1H, s).

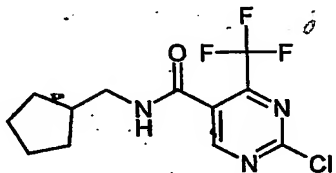
LC/MS, $t = 3.53$ min, Molecular ion observed $[MH^+]$ = 495 consistent with the molecular formula $C_{20}H_{20}F_6N_4O_2S$.

Example 183: 2-(5-Chloro-2-methylphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (cyclopentylmethyl)-amide

(a). To a solution of 2-chloro-4-trifluoromethyl-pyrimidin-5-carbonyl chloride (1.0 g, ex Maybridge) in dichloromethane (7 ml) at -2° was added a dropwise a solution of cyclopentanemethanamine hydrochloride (0.55 g) and triethylamine (1.4 ml) in dichloromethane (13 ml) and the solution stirred at 0° for 1 hour. Dichloromethane was removed under reduced pressure and ethyl acetate (20 ml) added. The solution was washed with 2N hydrochloric acid (3 x 15 ml), dried (MgSO₄), evaporated and triturated with isohexane to afford 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (cyclopentylmethyl)-amide (838 mg).

NMR (DMSO-d₆) δ 1.1-1.3 (2H, m), 1.45-1.65 (4H, m), 1.65-1.8 (2H, m), 2.07 (1H, quintuplet), 3.20 (2H, t), 8.78 (1H, t), 9.17 (1H, s).

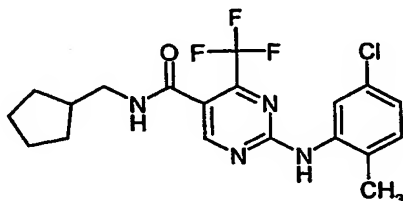
LC/MS, $t = 3.22$ min, Molecular ion observed $[M-H]^-$ = 306 consistent with the molecular formula $C_{12}H_{13}^{35}ClF_3N_3O$.



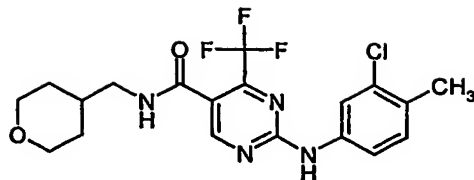
(b). In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclopentylmethylamide (47.5 mg) and 5-chloro-2-methylaniline (110 mg, ex Aldrich) afforded after stirring at reflux for 30 hours the title compound (41 mg).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.4-1.6 (4H, m), 1.65-1.75 (2H, m), 2.06 (1H, quintuplet), 2.20 (3H, s), 3.14 (2H, t), 7.19 (1H, d), 7.29 (1H, d), 7.48 (1H, s), 8.55 (1H, t), 8.63 (1H, s), 9.83 (1H, s).

LC/MS, $t = 3.68$ min, Molecular ion observed $[MH^+]$ = 413 consistent with the molecular formula $C_{19}H_{20}^{35}ClF_3N_4O$.



Example 184: 2-(3-Chloro-4-methylphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



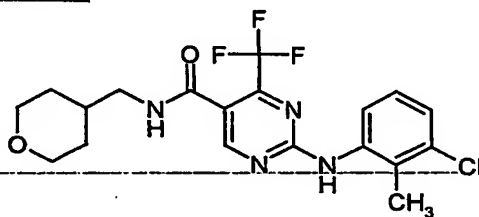
In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 3-chloro-4-methyl-aniline (109 mg) afforded, after stirring at reflux for 24 hours and purification by mass-directed autopreparation technique, the title compound (35 mg).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.61 (2H, d), 1.74 (1H, m), 2.28 (3H, s), 3.13 (2H, t), 3.27 (2H, t), 3.86 (2H, d of d), 7.31 (1H, d), 7.56 (1H, d), 7.94 (1H, s), 8.61 (1H, t), 8.79 (1H, s), 10.50 (1H, s).

LC/MS, Molecular ion observed $[MH^+] = 429$ consistent with the molecular formula

$C_{19}H_{20}^{35}ClF_3N_4O_2$.

Example 185: 2-(3-Chloro-2-methylphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide

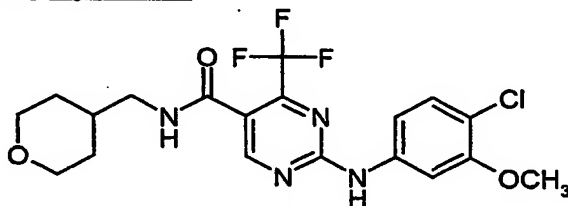


In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 3-chloro-2-methyl-aniline (109 mg, known compound CAS No 87-60-5) afforded, after stirring at reflux for 24 hours and purification by mass-directed autopreparation technique, the title compound (30 mg).

NMR (DMSO-d₆) δ 1.1-1.25 (2H, m), 1.59 (2H, d), 1.72 (1H, m), 2.21 (3H, s), 3.10 (2H, t), 3.26 (2H, t), 3.84 (2H, d of d), 7.24 (1H, t), 7.3 (2H, m), 8.56 (1H, t), 8.61 (1H, s), 9.99 (1H, s).

LC/MS, $t = 3.19$ min, Molecular ion observed $[MH^+] = 429$ consistent with the molecular formula $C_{19}H_{20}^{35}ClF_3N_4O_2$.

Example 186: 2-(4-Chloro-3-methoxyphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide

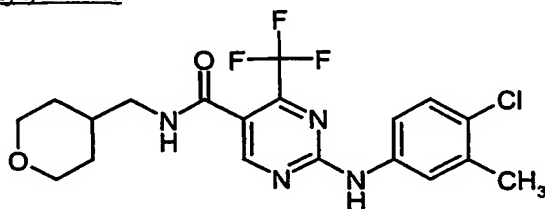


In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 4-chloro-3-methoxy-aniline (122 mg) afforded, after stirring at reflux for 24 hours and purification by mass-directed autopreparation technique, the title compound (33 mg).

NMR (DMSO-d₆) δ 1.1-1.25 (2H, m), 1.61 (2H, d), 1.73 (1H, m), 3.13 (2H, t), 3.27 (2H, t), 3.83 (3H, s), 3.86 (2H, d), 7.27 (1H, d), 7.37 (1H, d), 7.81 (1H, s), 8.63 (1H, t), 8.80 (1H, s), 10.50 (1H, s).

LC/MS, $t = 3.26$ min, Molecular ion observed $[MH^+] = 445$ consistent with the molecular formula $C_{19}H_{20}^{35}ClF_3N_4O_3$.

Example 187: 2-(4-Chloro-3-methylphenylamino)-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



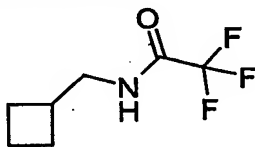
- 10 In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 4-chloro-3-methyl-aniline (109 mg, ex Lancaster) afforded, after stirring at reflux for 24 hours and purification by mass-directed autopreparation technique, the title compound (33 mg).

15 NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.61 (2H, d), 1.73 (1H, m), 2.31 (3H, s), 3.12 (2H, t), 3.27 (2H, t), 3.86 (2H, d), 7.37 (1H, d), 7.62 (1H, d), 7.72 (1H, s), 8.61 (1H, t), 8.77 (1H, s), 10.45 (1H, s).

LC/MS, $t = 3.41$ min, Molecular ion observed $[MH^+] = 429$ consistent with the molecular formula $C_{19}H_{20}^{35}ClF_3N_4O_2$.

20 **Example 188: 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-methyl-amide**

a) N-(Cyclobutylmethyl)-2,2,2-trifluoroacetamide



- 25 C-cyclobutyl-methylamine hydrochloride (1.82g) was added to a solution of N,N-diisopropylethylamine (4.14g) in dry tetrahydrofuran (30ml) at 0°C. The mixture was stirred at 0°C for 5mins then cooled to -20°C. A solution of trifluoroacetic anhydride (3.57g) in tetrahydrofuran (10ml) was added dropwise over 10mins and the mixture was then allowed to stir at room temperature for 1 hour. The solution was diluted with ether (100ml) and water (75ml),
- 30 separated and the organic layer washed with water, dilute hydrochloric acid, water and brine, dried (MgSO₄) and evaporated to give the title compound (2.63g)
- NMR (CDCl₃) δ 1.70 (2H, m excess), 1.93 (2H, m), 2.10 (2H, m), 2.53 (1H, m), 3.39 (2H, t), 6.2 (1H, br s).

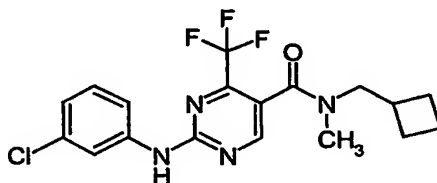
35 b) N-(Cyclobutylmethyl)-N-methylamine

N-(Cyclobutylmethyl)-2,2,2-trifluoroacetamide (2.62g) and iodomethane (3.6ml) were dissolved in dry acetone (75ml). Powdered potassium hydroxide (3.2g) was added and the mixture heated

at reflux for 5 mins. The excess iodomethane and acetone were removed under reduced pressure, water (75ml) added and the solution heated at reflux for 1 hour. The mixture was cooled and ether (75ml) added. The layers were separated and the organic layer was extracted with dilute hydrochloric acid (75ml). The aqueous extract was washed with ether, then made strongly basic with sodium hydroxide and extracted with ether (2 x 75ml). The extracts were dried (K_2CO_3) and evaporated to give the title compound (517mg)

NMR ($CDCl_3$) δ 1.3 (1H, m excess), 1.65 (2H, m), 1.9 (2H, m), 2.05 (2H, m), 2.45 (4H, m), 2.55 (2H, d).

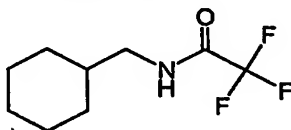
- 10 c) 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl – methyl-amide



- 15 To a solution of N-(cyclobutylmethyl)-N-methylamine (17mg) in dimethylformamide (1.5 ml) was added successively, 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg), N,N-diisopropylethylamine (38ul), 1-hydroxybenzotriazole hydrate (23 mg) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (25 mg). The solution was stirred overnight. Dimethylformamide was removed under reduced pressure and ethyl acetate (10 ml) added. The solution was washed sequentially with 10ml portions of water, saturated sodium bicarbonate solution, water, dilute hydrochloric acid, water and brine, dried ($MgSO_4$) and
- 20 evaporated to give the title compound (31 mg).
- NMR ($DMSO-d_6$) Rotamers in 60:40 ratio δ 1.5-2.1 (6H, m), 2.50 (0.4H, m excess), 2.65 (0.6H, m), 2.84 (1.8H, s), 2.94 (1.2H, s), 3.22 (0.4H, d), 3.50 (1.6H, br s), 7.09 (1H, d), 7.36 (1H, m), 7.66 (1H, m), 7.96 (1H, s), 8.76 (1H, d), 10.5 (1H, s).
- LC/MS $t = 3.66$ min, Molecular ion observed (MH^+) = 399 consistent with the molecular formula
- 25 $C_{18}H_{18}^{35}ClF_3N_4O$

Example 189; 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-methyl-amide.

- 30 a) N-(Cyclohexylmethyl)-2,2,2-trifluoroacetamide



- In a manner similar to Example 188a) cyclohexanemethanamine (2.83g) (Lancaster) gave the title compound (5.09g).
- 35 NMR ($CDCl_3$) δ 0.95 (2H, m), 1.22 (3H, m), 1.54 (1H, m excess), 1.70 (5H, m), 3.21 (2H, t), 6.3 (1H, br s).

- b) N-(Cyclohexylmethyl)-N-methylamine

In a manner similar to Example 188b) N-(cyclohexylmethyl)-2,2,2-trifluoroacetamide (2.98g) gave the title compound (1.41g).

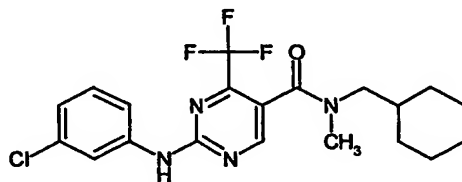
NMR (CDCl₃) δ 0.9 (2H, m), 1.23 (4H, m), 1.46 (1H, m excess), 1.72 (5H, m), 2.4 (5H, m).

- 5 c) 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl – methyl-amide.

In a manner similar to Example 188c) 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and N-(cyclohexylmethyl)-N-methylamine (21mg) gave the title compound.

- 10 NMR (DMSO-d₆) Rotamers in 63:37 ratio δ 0.65-1.30 (5H, m), 1.5-1.8 (6H, m), 2.87 (1.9H, s), 2.97 (1.1H, s), 3.03 (0.7H, d), 3.30 (1.3H, d excess), 7.09 (1H, d), 7.36 (1H, m), 7.66 (1H, d), 7.96 (1H, m), 8.73 (0.37H, s), 8.78 (0.63H, s), 10.6 (1H, s).

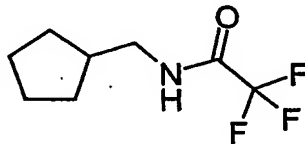
LC/MS t = 3.87 min, Molecular ion observed (MH⁺) = 427 consistent with the molecular formula C₂₀H₂₂³⁵ClF₃N₄O



15

Example 190: 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-methyl-amide

- a) N-(Cyclopentylmethyl)-2,2,2-trifluoroacetamide



20

In a manner similar to Example 188a) (cyclopentylmethyl)amine (1.02g) (Example 2) gave the title compound (1.47g).

NMR (CDCl₃) δ 1.21 (2H, m), 1.4 (4H, m), 1.78 (2H, m), 2.10 (1H, m), 3.31 (2H, t), 6.3 (1H, br s).

25

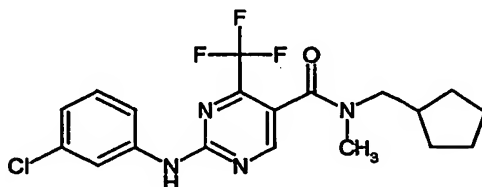
- b) N-(Cyclopentylmethyl)-N-methylamine hydrochloride

In a manner similar to Example 188b) N-(cyclopentylmethyl)-2,2,2-trifluoroacetamide (1.46g) gave, after treatment with hydrogen chloride in 1,4-dioxan, the title compound (0.77g).

NMR (D₂O) δ 1.12 (2H, m), 1.5 (4H, m), 1.75 (2H, m), 2.08 (1H, m), 2.61 (3H, s), 2.90 (2H, d).

30

- c) 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl – methyl-amide



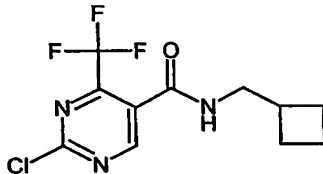
In a manner similar to Example 188c) 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and N-(cyclopentylmethyl)-N-methylamine hydrochloride (21 mg) together with an additional equivalent of N,N-diisopropylethylamine gave the title compound (42mg)

- 5 NMR (DMSO-d₆) Rotamers in 65:35 ratio δ 1.0-1.8 (8H, m), 2.13 (0.35H, m), 2.27 (0.65H, m), 2.88 (1.95H, s), 2.99 (1.05H, s), 3.14 (0.7H, d), 3.41 (1.3H, br s), 7.09 (1H, d), 7.36 (1H, t), 7.66 (1H, d), 7.96 (1H, m), 8.77 (1H, s), 10.6 (1H, s).
LC/MS $t = 3.77$ min, Molecular ion observed (MH^+) = 413 consistent with the molecular formula $C_{19}H_{20}^{35}ClF_3N_4O$

10

Example 191: 2-(5-Chloro-2-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide

a) 2-Chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



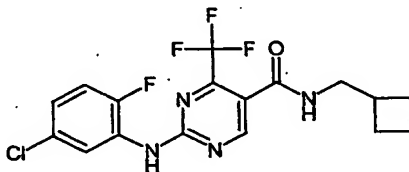
15

A mixture of 2-chloro-4-trifluoromethyl-pyrimidine-5-carbonyl chloride (613mg) (Maybridge) and C-cyclobutylmethylamine hydrochloride (304mg) in dry dichloromethane (10ml) was cooled to -30°C and N,N-diisopropylethylamine (958ul) was added dropwise. The mixture was stirred at room temp for 1 hour. Water (10ml) was added, the layers separated and the organic layer was washed sequentially with 10ml portions of water, dilute hydrochloric acid, water, dilute sodium bicarbonate solution and water, dried ($MgSO_4$) and evaporated. Purification by chromatography on silica gel (dichloromethane/ether 25:1) gave the title compound (449 mg).
NMR ($CDCl_3$) δ 1.75 (2H, m), 1.93 (2H, m), 2.10 (2H, m), 2.57 (1H, m), 3.50 (2H, t), 5.86 (1H, br s), 8.90 (1H, s).

20

25

b) 2-(5-Chloro-2-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



30

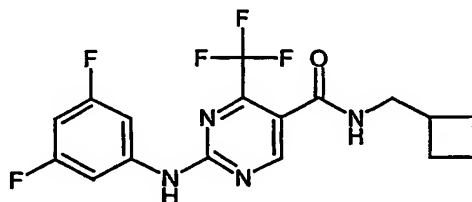
In a manner similar to Example 166, 5-chloro-2-fluoroaniline (109mg) (Avacado) and 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (44 mg) gave the title compound (45mg).

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 1.99 (2H, m), 2.47 (1H, m excess), 3.25 (2H, t), 7.3 (2H, m), 7.76 (1H, m), 8.56 (1H, t), 8.70 (1H, s), 10.2 (1H, s)

35

LC/MS $t = 3.52$ min, Molecular ion observed (MH^+) = 403 consistent with the molecular formula $C_{17}H_{15}^{35}ClF_4N_4O$

Example 192: 2-(3,5-Difluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide

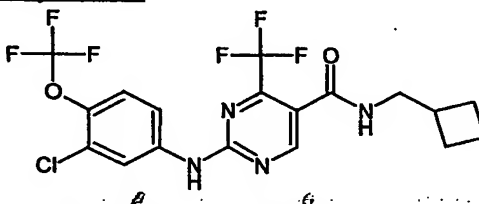


In a manner similar to Example 166, 3,5-difluoroaniline (97mg) (Lancaster) and 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (44 mg) gave the title compound (46mg).

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.27 (2H, t), 6.88 (1H, m), 7.55 (2H, m), 8.60 (1H, t), 8.83 (1H, s), 10.8 (1H, s)

LC/MS $t = 3.54$ min, Molecular ion observed (MH^+) = 387 consistent with the molecular formula $C_{17}H_{15}F_5N_4O$

Example 193: 2-(3-Chloro-4-trifluoromethoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide

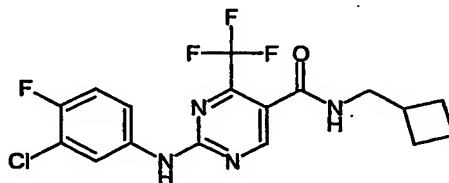


In a manner similar to Example 166, 3-chloro-4-trifluoromethoxy aniline (159mg) (Lancaster) and 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (44 mg) gave the title compound (59mg).

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.27 (2H, t), 7.56 (1H, d), 7.76 (1H, m), 8.16 (1H, d), 8.59 (1H, t), 8.81 (1H, s), 10.8 (1H, s)

LC/MS $t = 3.82$ min, Molecular ion observed (MH^+) = 469 consistent with the molecular formula $C_{18}H_{15}^{35}ClF_6N_4O_2$

Example 194: 2-(3-Chloro-4-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide

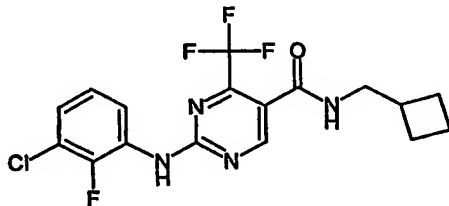


In a manner similar to Example 166, 3-chloro-4-fluoroaniline (109mg) (Lancaster) and 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (44 mg) gave the title compound (50mg).

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.27 (2H, t), 7.42 (1H, t), 7.67 (1H, m), 8.04 (1H, m), 8.57 (1H, t), 8.77 (1H, s), 10.6 (1H, s)

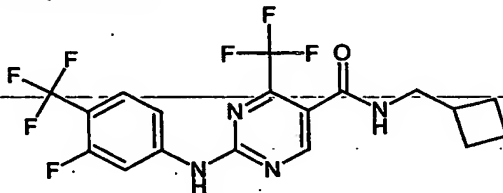
LC/MS $t = 3.60$ min, Molecular ion observed (MH^+) = 403 consistent with the molecular formula $C_{17}H_{15}^{35}ClF_4N_4O$

Example 195: 2-(3-Chloro-2-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



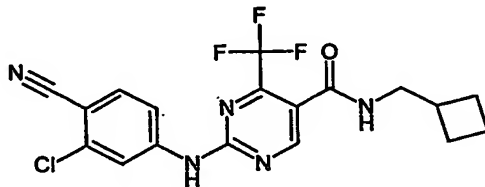
- 5 In a manner similar to Example 166, 3-chloro-2-fluoroaniline (109mg) (Acros) and 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (44 mg) gave the title compound (47mg).
 NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.23 (2H, t), 7.22 (1H, t), 7.42 (1H, t), 7.54 (1H, t), 8.55 (1H, t), 8.65 (1H, s), 10.2 (1H, s)
- 10 LC/MS $t = 3.49$ min, Molecular ion observed (MH^+) = 403 consistent with the molecular formula $C_{17}H_{15}^{35}ClF_4N_4O$

Example 196: 2-(3-Fluoro-4-trifluoromethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



- 15 In a manner similar to Example 166, 3-fluoro-4-trifluoromethylaniline (134mg) (ABCR) and 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid C-cyclobutylmethyl-amide (44 mg) gave the title compound (41mg).
 NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.26 (2H, t), 7.67 (1H, d), 7.75 (1H, t), 8.02 (1H, d), 8.62 (1H, t), 8.87 (1H, s), 11.0 (1H, s)
- 20 LC/MS $t = 3.71$ min, Molecular ion observed (MH^+) = 437 consistent with the molecular formula $C_{18}H_{15}F_7N_4O$

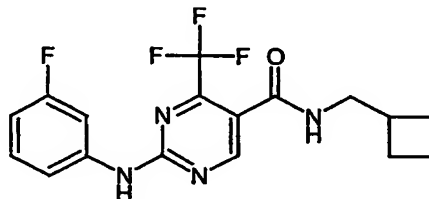
Example 197: 2-(3-Chloro-4-cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



- 25 In a manner similar to Example 166, 3-chloro-4-cyanoaniline (114mg) (Lancaster) and 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (44 mg) gave the title compound (26mg).
 NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.27 (2H, t), 7.83 (1H, m), 7.93 (1H, d), 8.24 (1H, s), 8.62 (1H, t), 8.89 (1H, s), 11.1 (1H, s)
- 30

LC/MS $t = 3.50$ min, Molecular ion observed (MH^+) = 410 consistent with the molecular formula $C_{18}H_{15}^{35}ClF_3N_5O$

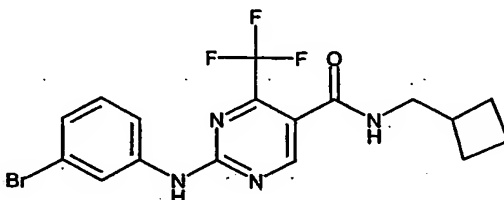
5 Example 198: 2-(3-Fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



In a manner similar to Example 188, 2-(3-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30 mg) and C-cyclobutylmethylamine hydrochloride (18mg) gave the title compound (31mg).

10 NMR (DMSO- d_6) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.26 (2H, t), 6.86 (1H, m), 7.37 (1H, m), 7.50 (1H, d), 7.76 (1H, m), 8.58 (1H, t), 8.78 (1H, s), 10.6 (1H, s)
LC/MS $t = 3.42$ min, Molecular ion observed (MH^+) = 369 consistent with the molecular formula $C_{17}H_{16}F_4N_4O$

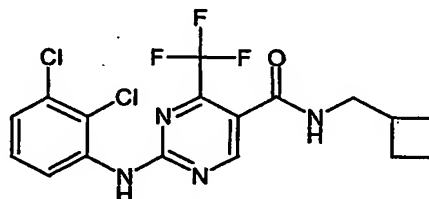
15 Example 199: 2-(3-Bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



In a manner similar to Example 188, 2-(3-bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and C-cyclobutylmethylamine hydrochloride (18mg) gave the title compound (33mg).

20 NMR (DMSO- d_6) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.26 (2H, t), 7.22 (1H, d), 7.31 (1H, t), 7.70 (1H, d), 8.10 (1H, t), 8.57 (1H, t), 8.78 (1H, s), 10.6 (1H, s)
LC/MS $t = 3.60$ min, Molecular ion observed (MH^+) = 431 consistent with the molecular formula $C_{17}H_{16}^{81}BrF_3N_4O$

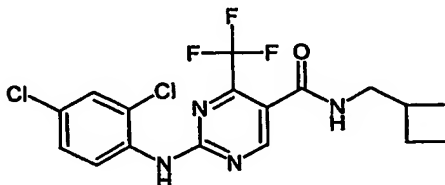
25 Example 200: 2-(2,3-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



30 In a manner similar to Example 188, 2-(2,3-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and C-cyclobutylmethylamine hydrochloride (18mg) gave the title compound (36mg).

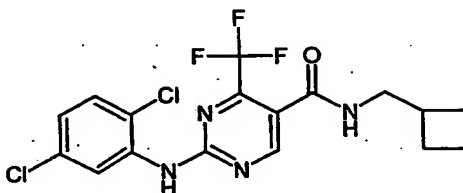
NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.24 (2H, t), 7.40 (1H, t), 7.54 (2H, m), 8.54 (1H, t), 8.63 (1H, s), 10.1 (1H, s)
 LC/MS $t = 3.61$ min, Molecular ion observed (MH^+) = 419 consistent with the molecular formula $C_{17}H_{15}^{35}Cl_2F_3N_4O$

5 Example 201: 2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



10 In a manner similar to Example 188, 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and C-cyclobutylmethylamine hydrochloride (18mg) gave the title compound (37mg).
 NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.24 (2H, t), 7.47 (1H, m), 7.58 (1H, d), 7.72 (1H, d), 8.54 (1H, t), 8.65 (1H, s), 10.0 (1H, s)
 LC/MS $t = 3.66$ min, Molecular ion observed (MH^+) = 419 consistent with the molecular formula $C_{17}H_{15}^{35}Cl_2F_3N_4O$

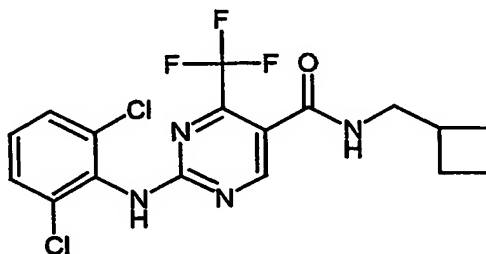
15 Example 202: 2-(2,5-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



20 In a manner similar to Example 188, 2-(2,5-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and C-cyclobutylmethylamine hydrochloride (18mg) gave the title compound (33mg).
 NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.24 (2H, t), 7.34 (1H, m), 7.58 (1H, d), 7.72 (1H, d), 8.55 (1H, t), 8.66 (1H, s), 10.0 (1H, s)
 LC/MS $t = 3.65$ min, Molecular ion observed (MH^+) = 419 consistent with the molecular formula $C_{17}H_{15}^{35}Cl_2F_3N_4O$

25

Example 203: 2-(2,6-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide

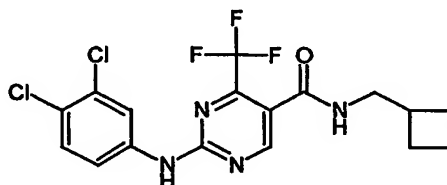


In a manner similar to Example 188, 2-(2,6-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and C-cyclobutylmethylamine hydrochloride (18mg) gave the title compound (35mg).

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.22 (2H, t), 7.39 (1H, t), 7.59 (2H, d), 8.56 (2H, m), 10.1 (1H, s).

LC/MS t = 3.38 min, Molecular ion observed (MH⁺) = 419 consistent with the molecular formula C₁₇H₁₅³⁵Cl₂F₃N₄O

Example 204: 2-(3,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide

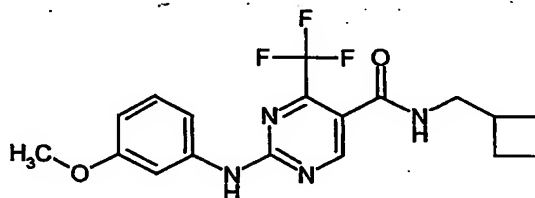


In a manner similar to Example 188, (3,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and C-cyclobutylmethylamine hydrochloride (18mg) gave the title compound (36mg).

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.26 (2H, t), 7.60 (1H, d), 7.69 (1H, m), 8.16 (1H, d), 8.58 (1H, t), 8.80 (1H, s), 10.7 (1H, s)

LC/MS t = 3.77 min, Molecular ion observed (MH⁺) = 419 consistent with the molecular formula C₁₇H₁₅³⁵Cl₂F₃N₄O

Example 205: 2-(3-Methoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide

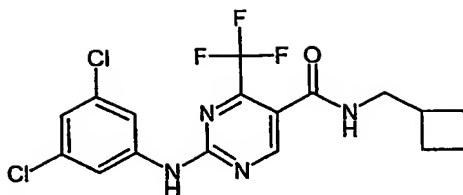


In a manner similar to Example 188, 2-(3-methoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (31 mg) and C-cyclobutylmethylamine hydrochloride (18mg) gave the title compound (38mg).

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.26 (2H, t), 3.74 (3H, s), 6.63 (1H, d), 7.24 (2H, m), 7.52 (1H, s), 8.56 (1H, t), 8.72 (1H, s), 10.4 (1H, s)

LC/MS t = 3.35 min, Molecular ion observed (MH⁺) = 381 consistent with the molecular formula C₁₈H₁₉F₃N₄O₂

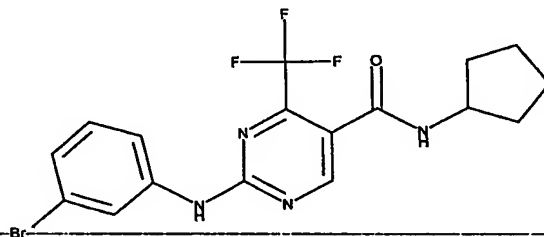
Example 206: 2-(3,5-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



In a manner similar to Example 188, 2-(3,5-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and C-cyclobutylmethylamine hydrochloride (18mg) gave the title compound (36mg).

- 5 NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.26 (2H, t), 7.60 (1H, d), 7.69 (1H, m), 8.16 (1H, d), 8.58 (1H, t), 8.80 (1H, s), 10.7 (1H, s)
LC/MS t = 3.84 min, Molecular ion observed (MH⁺) = 419 consistent with the molecular formula C₁₇H₁₅³⁵Cl₂F₃N₄O

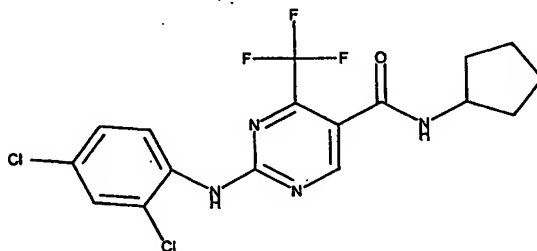
10 Example 207: 2-(3-Bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylamide



In a manner similar to Example 188, 2-(3-bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and cyclopentylamine (18mg) gave the title compound (28mg).

- 15 NMR (DMSO-d₆) δ 1.5 (4H, m), 1.66 (2H, m), 1.86 (2H, m), 4.16 (1H, m), 7.22 (1H, d), 7.31 (1H, t), 7.70 (1H, d), 8.10 (1H, t), 8.53 (1H, d), 8.79 (1H, s), 10.6 (1H, s)
LC/MS t = 3.39 min, Molecular ion observed (MH⁺) = 431 consistent with the molecular formula C₁₇H₁₆⁸¹BrF₃N₄O

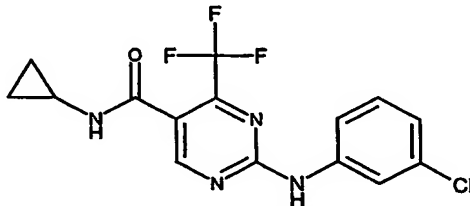
20 Example 208: 2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid N-cyclopentylamide



In a manner similar to Example 188, 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (26 mg) and cyclopentylamine (18mg) gave the title compound (21mg).

- 25 NMR (DMSO-d₆) δ 1.5 (4H, m), 1.63 (2H, m), 1.84 (2H, m), 4.14 (1H, m), 7.47 (1H, m), 7.56 (1H, d), 7.71 (1H, d), 8.50 (1H, d), 8.62 (1H, s), 10.0 (1H, s)
LC/MS t = 3.40 min, Molecular ion observed (MH⁺) = 419 consistent with the molecular formula C₁₇H₁₅³⁵Cl₂F₃N₄O

Example 209: 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopropylamide

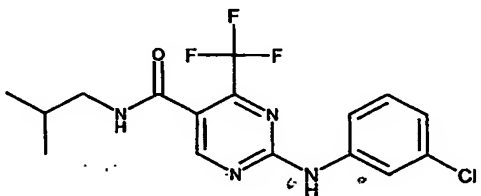


In a manner similar to Reference Example 1 (c) 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35mg) and cyclopropylamine (9mg, ex Lancaster) afforded the title compound (32mg).

NMR (DMSO-d₆) δ 0.49-0.52 (2H, m), 0.69-0.74 (2H, m), 2.78 (1H, m), 7.09 (1H, d), 7.36 (1H, t), 7.65 (1H, d), 7.95 (1H, s), 8.65 (1H, d), 8.80 (1H, s), 10.60 (1H, s)

LC/MS, $t = 3.25$ min, Molecular ion observed (MH^+) = 357 consistent with the molecular formula $C_{15}H_{12}N_4O F_3^{35}Cl$

Example 210: 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid N-(3,3-dimethylbutyl)-amide



In a manner similar to Reference Example 1 (c) 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (50mg) and 3,3-dimethylbutylamine (17mg, ex Aldrich) afforded the title compound (32mg).

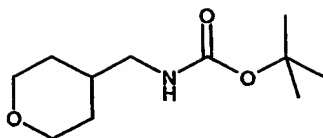
NMR (DMSO-d₆) δ 0.96 (6H, d), 1.85 (1H, m), 3.12 (2H, t), 7.16 (1H, d), 7.42 (1H, t), 7.71 (1H, d), 8.02 (1H, s), 8.65 (1H, t), 8.86 (1H, s), 10.70 (1H, s)

LC/MS, $t = 3.49$ min, Molecular ion observed (MH^+) = 373 consistent with the molecular formula $C_{16}H_{16}N_4O F_3^{35}Cl$

Example 211: 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid methyl-(tetrahydro-pyran-4-ylmethyl)-amide

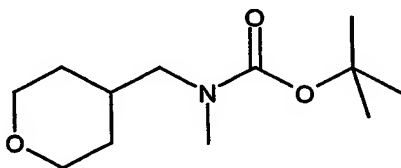
(a). To a solution of 4-aminomethyltetrahydropyran (500mg, ex Combi-Blocks, Inc.) in dichloromethane (10ml) at 0°C was added triethylamine (1.2ml) followed by a solution of di-tert-butyl dicarbonate (1.14g) in dichloromethane (4ml). The reaction was stirred at 0°C for 1h. Dichloromethane was removed under reduced pressure and ethyl acetate added (10ml). The solution was washed sequentially with 2N hydrochloric acid (10ml), water (10ml), 5% sodium bicarbonate solution (10ml), and water (10ml), dried ($MgSO_4$) and evaporated. The residue was purified by chromatography eluting with 2% MeOH/ CH_2Cl_2 , to afford N-(tetrahydro-pyran-4-ylmethyl)-carbamic acid tert-butyl ester (809mg).

NMR (DMSO-d₆) δ 1.15 (2H, m), 1.45 (9H, s), 1.80-1.95 (3H, d,m), 2.87 (2H, t), 3.30 (2H, t), 3.90 (2H, d,d), 6.95 (1H, t).



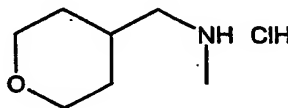
(b). To a solution of N-(tetrahydro-pyran-4-ylmethyl)-carbamic acid tert-butyl ester (800mg) in THF (10ml) at room temperature under nitrogen was added 60% sodium hydride (164mg, ex Aldrich) portionwise. The reaction was stirred until effervescence had ceased and then methyl iodide (280 μ l, ex Lancaster) was added. Stirring was continued at room temperature overnight. THF was removed under reduced pressure and ethyl acetate was added (10ml). This was washed three times with water (10ml), dried (MgSO_4) and evaporated. The residue was purified by chromatography eluting with 3% MeOH/ CH_2Cl_2 , to afford N-methyl-N-(tetrahydro-pyran-4-ylmethyl)-carbamic acid tert-butyl ester (745mg).

10 NMR (DMSO- d_6) δ 1.15 (2H, m), 1.45 (9H, s), 1.50 (2H, m), 1.80 (1H, m) 2.80 (3H, d), 3.08 (2H, d), 3.28 (2H, t), 3.85 (2H, d).



15 (c). A solution of N-methyl-N-(tetrahydro-pyran-4-ylmethyl)-carbamic acid tert-butyl ester (740mg) in 4N hydrochloric acid in 1,4-dioxan (10ml, ex Aldrich) was stirred at room temperature for 1h. The dioxan was removed under reduced pressure and the residue triturated with ether. The solid was filtered onto a sinter, washed with ether and dried, to afford N-methyl-N-(tetrahydro-pyran-4-ylmethyl)-amine hydrochloride (460mg).

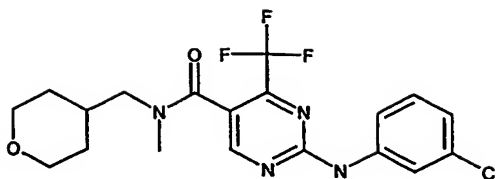
20 NMR (DMSO- d_6) δ 1.15 (2H, m), 1.65 (2H, d), 1.95 (1H, m) 2.50 (3H, d), 2.80 (2H, d), 3.30 (2H, t), 3.85 (2H, d), 9.0 (2H, s).



25 (d). In a manner similar to Reference Example 1 (c) 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (50mg) and N-methyl-N-(tetrahydro-pyran-4-yl methyl) amine hydrochloride (39mg) afforded, after Biotage chromatography over silica gel, eluting with 1% MeOH/ CH_2Cl_2 , the title compound (33mg).

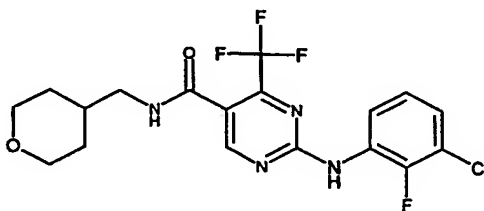
30 NMR (DMSO- d_6) Rotamers in 65:35 ratio δ 1.05 (0.7H, m), 1.23 (1.3H, m), 1.45 (0.7H, d), 1.58 (1.3H, d), 1.85 (0.35H, m), 2.0 (0.65H, m), 2.89 (1.95H, s), 2.98 (1.05H, s), 3.10-3.40 (4H, m), 3.80 (0.7H, d), 3.88 (1.3H, d), 7.10 (1H, d), 7.36 (1H, t), 7.65 (1H, t), 7.97 (1H, s), 8.75 (0.35H, s), 8.80 (0.65H, s), 10.6 (1H, s)

LC/MS, $t = 3.29$ min, Molecular ion observed (MH^+) = 429 consistent with the molecular formula $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_2\text{F}_3^{35}\text{Cl}$



Example 212: 2-(2-Fluoro-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide

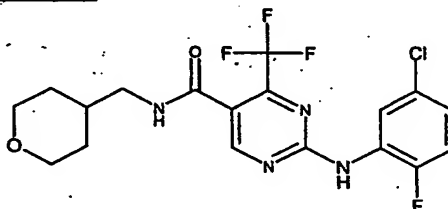
5



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (100mg) and 2-fluoro-3-chloroaniline (225mg, ex Acros) afforded the title compound (85mg) after purification by trituration with isohexane.

- 10 NMR (DMSO-d₆) δ 1.14-1.23 (2H, m), 1.6 (2H, d), 1.72 (1H, m), 3.1 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.24 (1H, t), 7.42 (1H, t), 7.55 (1H, t), 8.61 (1H, t), 8.70 (1H, s), 10.20 (1H, s)
LC/MS, t = 3.14 min, Molecular ion observed (MH⁺) = 433 consistent with the molecular formula C₁₈H₁₇N₄O₂F₄³⁵Cl

- 15 **Example 213: 2-(2-Fluoro-5-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide**

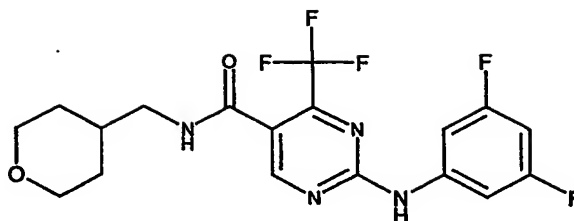


In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (100mg) and 2-fluoro-5-chloroaniline (225mg, ex Avocado) afforded the title compound (96mg) after purification by trituration with isohexane.

- 20 NMR (DMSO-d₆) δ 1.17-1.23 (2H, m), 1.6 (2H, d), 1.72 (1H, m), 3.1 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.27-7.37 (2H, t,m), 7.76 (1H, dd), 8.62 (1H, t), 8.73 (1H, s), 10.15 (1H, s)
LC/MS, t = 3.15 min, Molecular ion observed (MH⁺) = 433 consistent with the molecular formula C₁₈H₁₇N₄O₂F₄³⁵Cl

25

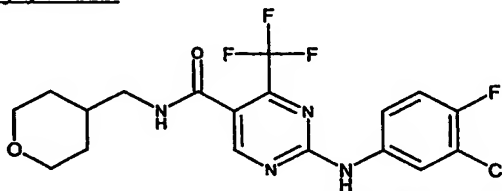
Example 214: 2-(3,5-Difluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Example 167, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (100mg) and 3,5-difluoroaniline (199mg, ex Lancaster) afforded the title compound (98mg) after purification by trituration with isohexane.

- 5 NMR (DMSO- d_6) δ 1.18-1.25 (2H, m), 1.61 (2H, d), 1.74 (1H, m), 3.13 (2H, t), 3.27 (2H, m), 3.85 (2H, d), 6.88 (1H, t), 7.52 7.55 (2H, m), 8.66 (1H, t), 8.86 (1H, s), 10.80 (1H, s)
LC/MS, $t = 3.18$ min, Molecular ion observed (MH^+) = 417 consistent with the molecular formula $C_{18}H_{17}N_4O_2F_5$

- 10 Example 217: 2-(4-Fluoro-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide

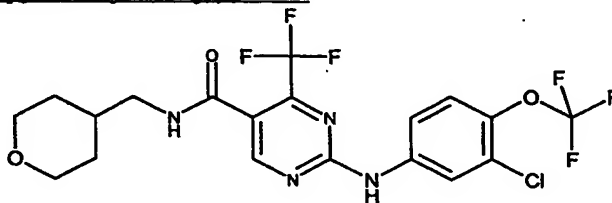


In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (100mg) and 4-fluoro-3-chloroaniline (225mg, ex

- 15 Lancaster) afforded the title compound (134mg) after purification by trituration with isohexane.
NMR (DMSO- d_6) δ 1.18-1.23 (2H, m), 1.61 (2H, d), 1.75 (1H, m), 3.1 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.42 (1H, t), 7.65 (1H, m), 8.05 (1H, dd), 8.63 (1H, t), 8.80 (1H, s), 10.65 (1H, s)
LC/MS, $t = 3.25$ min, Molecular ion observed (MH^+) = 433 consistent with the molecular formula $C_{18}H_{17}N_4O_2F_4^{35}Cl$

20

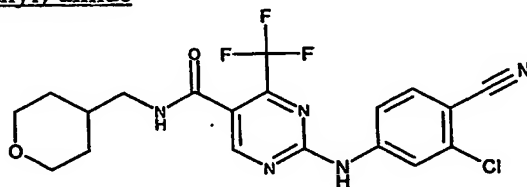
Example 216: 2-(4-Trifluoromethoxy-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (100mg) and 4-trifluoromethoxy-3-chloroaniline (327mg, ex Lancaster) afforded the title compound (135mg) after purification by trituration with isohexane.

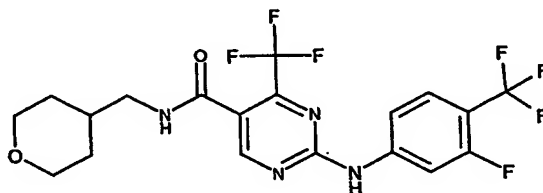
- 25 NMR (DMSO- d_6) δ 1.18-1.23 (2H, m), 1.61 (2H, d), 1.74 (1H, m), 3.13 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.57 (1H, d), 7.75 (1H, dd), 8.14 (1H, d), 8.63 (1H, t), 8.84 (1H, s), 10.74 (1H, s)
30 LC/MS, $t = 3.51$ min, Molecular ion observed (MH^+) = 499 consistent with the molecular formula $C_{19}H_{17}N_4O_3F_6^{35}Cl$

Example 217: 2-(4-Cyano-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



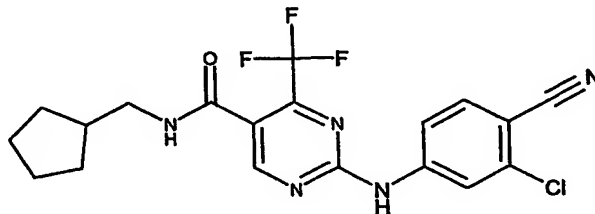
- 5 In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (100mg) and 4-cyano-3-chloroaniline (236mg, ex Lancaster) afforded the title compound (8mg). Sample purified by mass directed auto-prep. LC/MS, $t = 3.51$ min, Molecular ion observed (MH^+) = 440 consistent with the molecular formula $C_{19}H_{17}N_5O_2F_3^{35}Cl$

10 Example 218: 2-(4-Trifluoromethyl-3-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



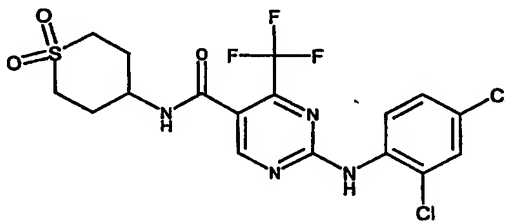
- 15 In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (100mg) and 4-trifluoromethyl-3-fluoroaniline (277mg, ex ABCR) afforded the title compound (125mg) after purification by trituration with isohexane. NMR (DMSO- d_6) δ 1.16-1.25 (2H, m), 1.61 (2H, d), 1.73 (1H, m), 3.14 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.67 (1H, d), 7.75 (1H, t), 8.02 (1H, d), 8.68 (1H, t), 8.90 (1H, s), 11.00 (1H, s) LC/MS, $t = 3.38$ min, Molecular ion observed (MH^+) = 467 consistent with the molecular formula $C_{19}H_{17}N_4O_2F_7$
- 20

Example 219: 2-(4-Cyano-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethylamide



- 25 In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethylamide (70mg) and 4-cyano-3-chloroaniline (173mg, ex Lancaster) afforded the title compound (125mg). Purified by chromatography eluting with 1:1 ethyl acetate:hexane. NMR (DMSO- d_6) δ 1.20-1.25 (2H, m), 1.48-1.73 (6H, m), 2.08 (1H, m), 3.18 (2H, t), 7.83 (1H, dd), 7.84 (1H, d), 8.24 (1H, d), 8.66 (1H, t), 8.90 (1H, s), 11.10 (1H, s) LC/MS, $t = 3.68$ min, Molecular ion observed (MH^+) = 424 consistent with the molecular formula $C_{19}H_{17}N_5O_2F_3^{35}Cl$
- 30

Example 220: 2-(2,4-Dichloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (1,1-dioxo-hexahydro-1 β - thiopyran-4-yl)-amide

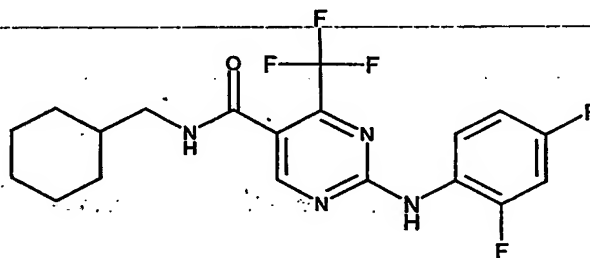


5

In a manner similar to Reference Example 1 (c) 2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (50mg) and (1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)amine hydrochloride (40mg) (Ref. WO 02/18380) afforded the title compound (64mg). Purified by chromatography eluting with 2% MeOH/CH₂Cl₂.

10 NMR (DMSO-d₆) δ 1.97 (2H, m), 2.13 (2H, m), 3.13 (2H, m), 3.27 (2H, m), 4.10 (1H, m), 7.47 (1H, dd), 7.56 (1H, d), 7.72 (1H, d), 8.67 (1H, t), 8.7 (1H, s), 10.05 (1H, s)
LC/MS, t = 3.22 min, Molecular ion observed (MH⁺) = 483 consistent with the molecular formula C₁₇H₁₅N₄O₃F₃³⁵Cl₂S

15 **Example 221: 2-(2,4-Difluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide**



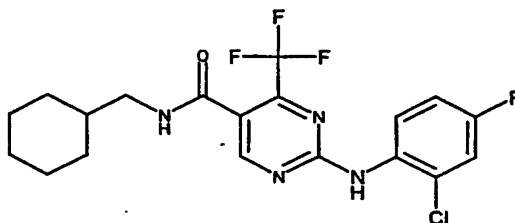
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (80mg) and 2,4-difluoroaniline (160mg, ex Lancaster) afforded the title compound (77mg) after purification by trituration with isohexane / diethylether.

20

NMR (DMSO-d₆) δ 0.89-0.95 (2H, m), 1.15-1.20 (3H, m), 1.46-1.47 (1H, m), 1.60-1.72 (5H, m), 3.05 (2H, t), 7.10 (1H, t), 7.35 (1H, m), 7.52 (1H, m), 8.53 (1H, t), 8.62 (1H, s), 10.00 (1H, s)
LC/MS, t = 3.63 min, Molecular ion observed (MH⁺) = 433 consistent with the molecular formula C₁₉H₁₉N₄O F₅

25

Example 222: 2-(2-Chloro-4-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide

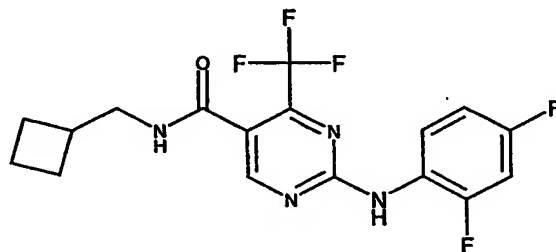


In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (80mg) and 2-chloro-4-fluoroaniline (181mg, ex Lancaster) afforded the title compound (91mg).

NMR (DMSO-d₆) δ 0.89-0.95 (2H, m), 1.15-1.20 (3H, m), 1.44-1.46 (1H, m), 1.62-1.72 (5H, m), 3.05 (2H, t), 7.27 (1H, m), 7.55 (2H, m), 8.52 (1H t), 8.60 (1H, s), 10.00 (1H, s)

LC/MS, t = 3.73 min, Molecular ion observed (MH⁺) = 431 consistent with the molecular formula C₁₉H₁₉N₄O F₄³⁵Cl

Example 223: 2-(2,4-Difluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide

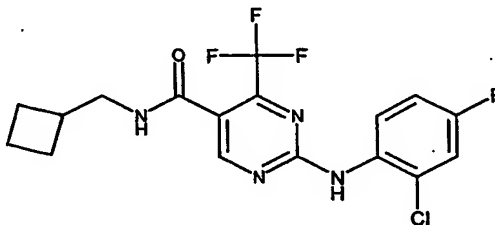


In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (80mg) and 2,4-difluoroaniline (198mg, ex Lancaster) afforded the title compound (82mg) after purification by trituration with isohexane / diethylether.

NMR (DMSO-d₆) δ 1.67-2.01 (6H, m), 2.47 (1H, m), 3.23 (2H, t), 7.10 (1H, t), 7.35 (1H, m), 7.52 (1H, m), 8.53 (1H t), 8.62 (1H, s), 10.00 (1H, s)

LC/MS, t = 3.40 min, Molecular ion observed (MH⁺) = 386 consistent with the molecular formula C₁₇H₁₅N₄O F₅

Example 224: 2-(2-Chloro-4-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide

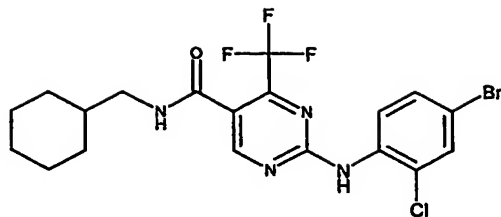


In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (80mg) and 2-chloro-4-fluoroaniline (198mg, ex Lancaster) afforded the title compound (80mg) after purification by trituration with 2N hydrochloric acid.

NMR (DMSO-d₆) δ 1.67-2.00 (6H, m), 2.46 (1H, m), 3.23 (2H, t), 7.27 (1H, m), 7.55 (2H, m), 8.52 (1H t), 8.58 (1H, s), 9.90 (1H, s)

LC/MS, t = 3.51 min, Molecular ion observed (MH⁺) = 403 consistent with the molecular formula C₁₇H₁₅N₄O F₄³⁵Cl

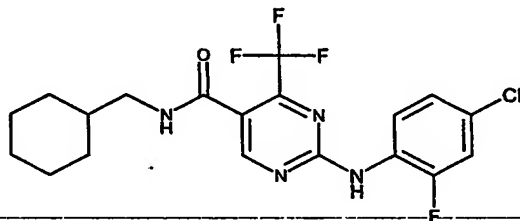
Example 225: 2-(2-Chloro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (80mg) and 2-chloro-4-bromoaniline (257 mg, ex Lancaster) afforded the title compound (96mg) after purification by trituration with 2N hydrochloric acid.

- 5 NMR (DMSO-d₆) δ 0.89-0.95 (2H, m), 1.15-1.20 (3H, m), 1.44-1.46 (1H, m), 1.62-1.72 (5H, m), 3.05 (2H, t), 7.52 (1H, d), 7.58 (1H, dd), 7.82 (1H, d), 8.55 (1H t), 8.63 (1H, s), 10.00 (1H, s)
LC/MS, t = 3.97 min, Molecular ion observed (MH⁺) = 493 consistent with the molecular formula C₁₉H₁₉N₄O F₃³⁵Cl⁸¹Br

- 10 Example 226: 2-(2-Fluoro-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide

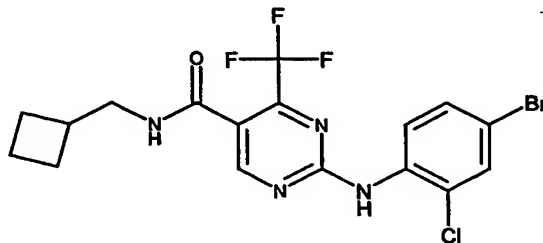


In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (80mg) and 2-fluoro-4-chloroaniline (180mg, ex Lancaster) afforded the title compound (73mg) after purification by trituration with 2N hydrochloric acid.

- 15 NMR (DMSO-d₆) δ 0.95-0.98 (2H, m), 1.15-1.20 (3H, m), 1.44-1.46 (1H, m), 1.66-1.72 (5H, m), 3.05 (2H, t), 7.31 (1H, d), 7.53 (1H, dd), 7.60 (1H, t), 8.55 (1H t), 8.66 (1H, s), 10.00 (1H, s)
LC/MS, t = 3.79 min, Molecular ion observed (MH⁺) = 431 consistent with the molecular formula C₁₉H₁₉N₄O F₄³⁵Cl

20

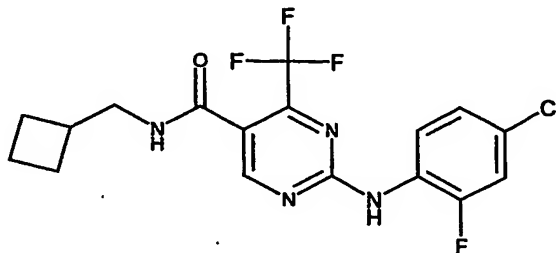
- Example 227: 2-(2-Chloro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (80mg) and 2-chloro-4-bromoaniline (281mg, ex Lancaster) afforded the title compound (103mg) after purification by trituration with 2N hydrochloric acid.

- 25 NMR (DMSO-d₆) δ 1.67-2.00 (6H, m), 2.45 (1H, m), 3.23 (2H, t), 7.50 (1H, d), 7.58 (1H, dd), 7.82 (1H, d), 8.53 (1H t), 8.61 (1H, s), 10.00 (1H, s)
LC/MS, t = 3.77 min, Molecular ion observed (MH⁺) = 465 consistent with the molecular formula C₁₇H₁₅N₄O F₃³⁵Cl⁸¹Br
- 30

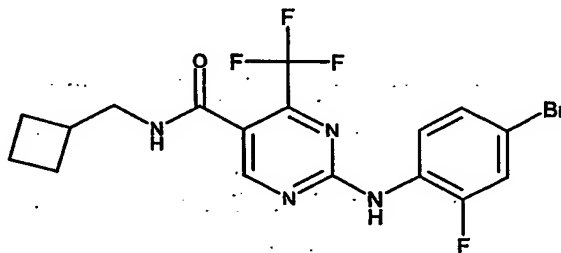
Example 228: 2-(2-Fluoro-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



- 5 In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (80mg) and 2-fluoro-4-chloroaniline (198mg, ex Lancaster) afforded the title compound (94mg) after purification by trituration with 2N hydrochloric acid.
NMR (DMSO-d₆) δ 1.67-2.08 (6H, m), 2.45 (1H, m), 3.23 (2H, t), 7.31 (1H, d), 7.53 (1H, dd), 7.60 (1H, t), 8.53 (1H t), 8.64 (1H, s), 10.00 (1H, s)
- 10 LC/MS, $t = 3.59$ min, Molecular ion observed (MH^+) = 403 consistent with the molecular formula $C_{17}H_{15}N_4O F_4^{35}Cl$

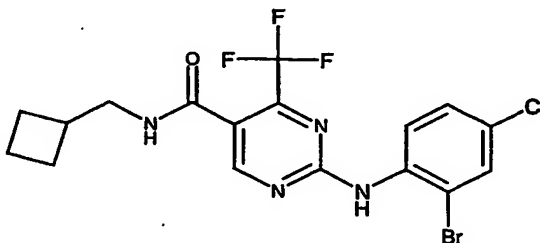
Example 229: 2-(2-Fluoro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide

15



- In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (80mg) and 2-fluoro-4-bromoaniline (259mg, ex Lancaster) afforded the title compound (95mg) after purification by trituration with 2N hydrochloric acid.
- 20 NMR (DMSO-d₆) δ 1.67-2.00 (6H, m), 2.45 (1H, m), 3.23 (2H, t), 7.43 (1H, d), 7.54 (1H, t), 7.63 (1H, dd), 8.53 (1H t), 8.64 (1H, s), 10.00 (1H, s)
- LC/MS, $t = 3.63$ min, Molecular ion observed (MH^+) = 449 consistent with the molecular formula $C_{17}H_{15}N_4O F_4^{81}Br$

- 25 Example 230: 2-(2-Bromo-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



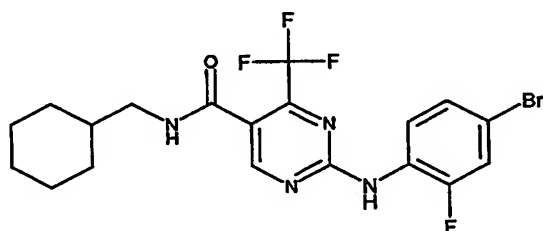
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (80mg) and 2-bromo-4-chloroaniline (281mg, ex Lancaster) afforded the title compound (105mg) after purification by trituration with 2N hydrochloric acid.

NMR (DMSO-d₆) δ 1.67-2.08 (6H, m), 2.45 (1H, m), 3.23 (2H, t), 7.52 (2H, m), 7.85 (1H, s),

5 8.53 (1H t), 8.60 (1H, s), 10.00 (1H, s)

LC/MS, $t = 3.75$ min, Molecular ion observed (MH^+) = 465 consistent with the molecular formula $C_{17}H_{15}N_4O F_3 ^{35}Cl ^{81}Br$

10 Example 231 2-(2-Fluoro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (80mg) and 2-fluoro-4-bromoaniline (236mg, ex Lancaster) afforded the

15 title compound (96mg) after purification by trituration with 2N hydrochloric acid.

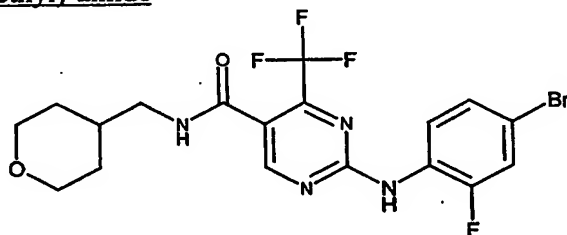
NMR (DMSO-d₆) δ 0.90-0.92 (2H, m), 1.15-1.20 (3H, m), 1.44-1.46 (1H, m), 1.63-1.72 (5H, m),

3.05 (2H, t), 7.44 (1H, d), 7.55 (1H, t), 7.64 (1H, dd), 8.55 (1H t), 8.66 (1H, s), 10.00 (1H, s)

LC/MS, $t = 3.83$ min, Molecular ion observed (MH^+) = 477 consistent with the molecular formula $C_{19}H_{19}N_4O F_4 ^{81}Br$

20

Example 232: 2-(2-Fluoro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid

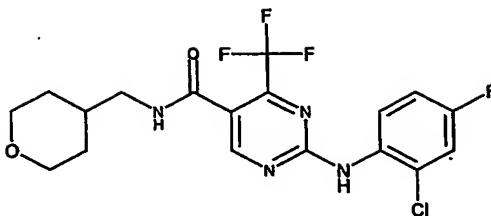
25 (tetrahydro-pyran-4-ylmethyl)-amide (80mg) and 2-fluoro-4-bromoaniline (235mg, ex Lancaster) afforded the title compound (100mg) after purification by trituration with 2N hydrochloric acid.

NMR (DMSO-d₆) δ 1.16-1.23 (2H, m), 1.60 (2H, d), 1.71 (1H, m), 3.1 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.43 (1H, d), 7.55 (1H, t), 7.64 (1H, dd), 8.60 (1H, t), 8.65 (1H, s), 10.10 (1H, s)

LC/MS, $t = 3.28$ min, Molecular ion observed (MH^+) = 479 consistent with the molecular formula

30 $C_{18}H_{17}N_4O_2 F_4 ^{81}Br$

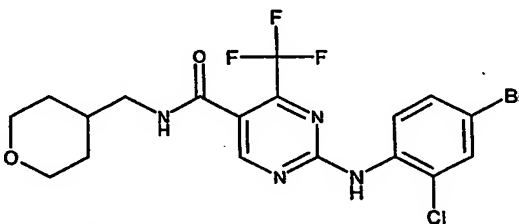
Example 233: 2-(2-Chloro-4-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (80mg) and 2-chloro-4-fluoroaniline (180mg, ex Lancaster) afforded the title compound (95mg) after purification by trituration with 2N hydrochloric acid.

- 5 NMR (DMSO-d₆) δ 1.14-1.23 (2H, m), 1.59 (2H, d), 1.71 (1H, m), 3.1 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.27 (1H, m), 7.55 (2H, m), 8.58 (1H, t), 8.61 (1H, s), 10.00 (1H, s)
LC/MS, t = 3.14 min, Molecular ion observed (MH⁺) = 433 consistent with the molecular formula C₁₈H₁₇N₄O₂F₄³⁵Cl

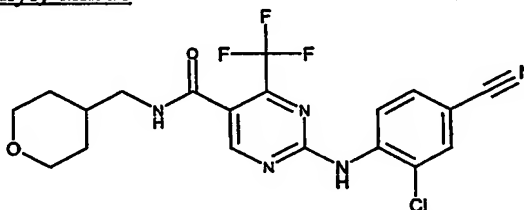
- 10 Example 234: 2-(2-Chloro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (80mg) and 2-chloro-4-bromoaniline (255mg, ex Lancaster) afforded the title compound (102mg) after purification by trituration with 2N hydrochloric acid.

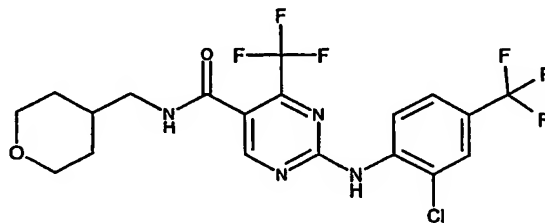
- 15 NMR (DMSO-d₆) δ 1.14-1.23 (2H, m), 1.58 (2H, d), 1.72 (1H, m), 3.1 (2H, t), 3.28 (2H, m), 3.84 (2H, d), 7.51 (1H, d), 7.59 (1H, dd), 7.82 (1H, d), 8.58 (1H, t), 8.63 (1H, s), 10.00 (1H, s)
LC/MS, t = 3.42 min, Molecular ion observed (MH⁺) = 495 consistent with the molecular formula C₁₈H₁₇N₄O₂F₃³⁵Cl⁸¹Br
- 20

Example 235: 2-(2-Chloro-4-cyano-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



- 25 In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (80mg) and 2-chloro-4-cyanoaniline (188mg, ex Lancaster) afforded the title compound (22mg). Sample purified by mass directed auto-prep.
NMR (DMSO-d₆) δ 1.14-1.23 (2H, m), 1.59 (2H, d), 1.72 (1H, m), 3.12 (2H, t), 3.23 (2H, m), 3.85 (2H, d), 7.87 (1H, d), 7.92 (1H, d), 8.14 (1H, s), 8.65 (1H, t), 8.75 (1H, s), 10.20 (1H, s)
LC/MS, t = 3.11 min, Molecular ion observed (MH⁺) = 440 consistent with the molecular formula C₁₉H₁₇N₅O₂F₃³⁵Cl
- 30

Example 236: 2-(2-Chloro-4-trifluoromethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



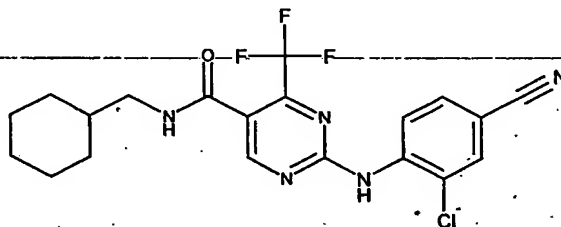
5

In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (80mg) and 2-chloro-4-trifluoromethylaniline (241mg, ex Lancaster) afforded the title compound (48mg). Sample purified by mass directed auto-prep.

10 NMR (DMSO-d₆) δ 1.17-1.23 (2H, m), 1.59 (2H, d), 1.72 (1H, m), 3.12 (2H, t), 3.23 (2H, m), 3.85 (2H, d), 7.77 (1H, d), 7.88 (1H, d), 7.96 (1H, s), 8.63 (1H, t), 8.72 (1H, s), 10.15 (1H, s) LC/MS, t = 3.47 min, Molecular ion observed (MH⁺) = 483 consistent with the molecular formula C₁₉H₁₇N₄O₂F₆³⁵Cl

Example 237: 2-(2-Chloro-4-cyano-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide

15

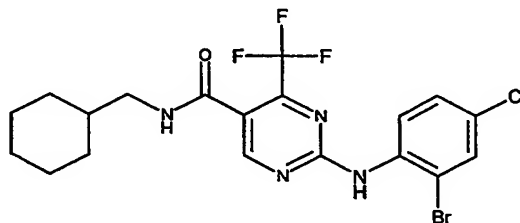


In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (80mg) and 2-chloro-4-cyanoaniline (189mg, ex Lancaster) afforded the title compound (15mg). Sample purified by mass directed auto-prep.

20 NMR (DMSO-d₆) δ 0.90 (2H, m), 1.15-1.23 (3H, m), 1.44-1.46 (1H, m), 1.67-1.73 (5H, m), 3.06 (2H, t), 7.87 (1H, dd), 7.92 (1H, d), 8.14 (1H, d), 8.58 (1H t), 8.74 (1H, s), 10.10 (1H, s) LC/MS, t = 3.67 min, Molecular ion observed (MH⁺) = 438 consistent with the molecular formula C₂₀H₁₉N₅O F₃³⁵Cl

Example 238: 2-(2-Bromo-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide

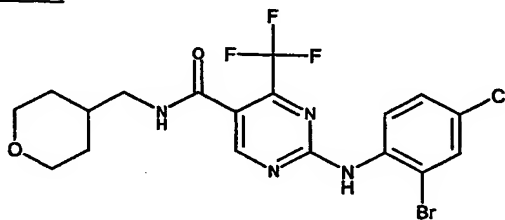
25



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (80mg) and 2-bromo-4-chloroaniline (257mg, ex Lancaster) afforded the title compound (23mg). Sample purified by mass directed auto-prep.

- 5 NMR (DMSO-d₆) δ 0.89-0.95 (2H, m), 1.15-1.20 (3H, m), 1.44-1.46 (1H, m), 1.62-1.72 (5H, m), 3.04 (2H, t), 7.52 (2H, m), 7.85 (1H, d), 8.53 (1H, t), 8.61 (1H, s), 10.00 (1H, s)
LC/MS, $t = 3.94$ min, Molecular ion observed (MH^+) = 493 consistent with the molecular formula $C_{19}H_{19}N_4O F_3^{35}Cl^{81}Br$

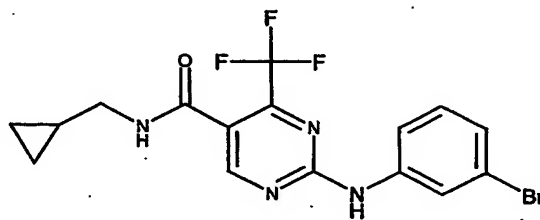
10 Example 239: 2-(2-Bromo-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (80mg) and 2-bromo-4-chloroaniline (255mg, ex Lancaster) afforded the title compound (6mg). Sample purified by mass directed auto-prep.

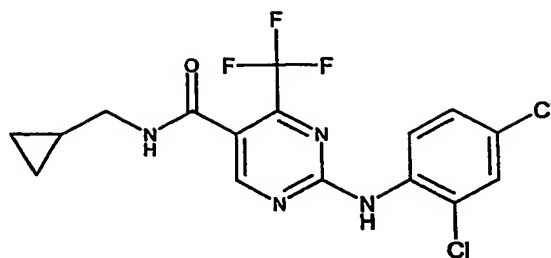
- 15 NMR (DMSO-d₆) δ 1.14-1.23 (2H, m), 1.58 (2H, d), 1.72 (1H, m), 3.1 (2H, t), 3.28 (2H, m), 3.84 (2H, d), 7.50 (2H, m), 7.82 (1H, d), 8.58 (1H, t), 8.63 (1H, s), 10.00 (1H, s)
LC/MS, $t = 3.40$ min, Molecular ion observed (MH^+) = 495 consistent with the molecular formula $C_{18}H_{17}N_4O_2 F_3^{35}Cl^{81}Br$

20 Example 240: 2-(3-Bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopropylmethyl-amide



- 25 In a manner similar to Reference Example 1 (c) 2-(3-bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (80mg) and cyclopropylmethylamine (19mg, ex Lancaster) afforded the title compound (24mg). Sample purified by mass directed auto-prep.
NMR (DMSO-d₆) δ 0.22 (2H, m), 0.45 (2H, m), 1.67 (1H, m), 3.13 (2H, t), 7.23 (1H, d), 7.30 (1H, t), 7.72 (1H, d), 8.10 (1H, m), 8.68 (1H, t), 8.80 (1H, s), 10.60 (1H, s)
30 LC/MS, $t = 3.49$ min, Molecular ion observed (MH^+) = 417 consistent with the molecular formula $C_{16}H_{14}N_4O F_3^{81}Br$

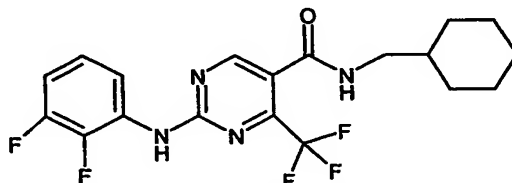
35 Example 241: 2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopropylmethyl-amide



In a manner similar to Reference Example 1 (c) 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (80mg) and cyclopropylmethylamine (19mg, ex Lancaster) afforded the title compound (58mg).

- 5 NMR (DMSO-d₆) δ 0.22 (2H, m), 0.45 (2H, m), 1.67 (1H, m), 3.13 (2H, t), 7.23 (1H, d), 7.30 (1H, t), 7.72 (1H, d), 8.10 (1H, m), 8.68 (1H, t), 8.80 (1H, s), 10.60 (1H, s)
LC/MS, $t = 3.56$ min, Molecular ion observed (MH^+) = 405 consistent with the molecular formula $C_{16}H_{13}N_4O F_3^{35}Cl$

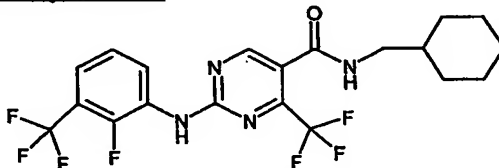
- 10 Example 242: 2-(2,3-Difluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide.



To a solution of 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (Example 166a) (50mg) in 1,4-dioxan (1ml) was added 2,3-difluoroaniline (Aldrich) (113mg) and the mixture was stirred at reflux for 47 hours using a Radleys Greenhouse Parallel Synthesiser. The dioxan was removed using a nitrogen blow down unit. The residue was taken up into methanol (0.5ml) and dimethylsulfoxide (0.5ml) and purified using a mass directed auto-preparative system to give the title compound (16mg)

- 15 NMR (Chloroform-d₆) δ 0.94-1.08 (2H, m), 1.15-1.34 (3H, m), 1.5-1.6 (>1H, m & water) 1.65-1.73 (1H, m), 1.73-1.83 (4H, m), 3.30 (2H, t), 5.91 (1H, bs) 6.88- 6.98 (1H, m) 7.08-7.1 (1H, m), 7.66 (1H, bs), 8.16-8.25 (1H, m), 8.75 (1H, s).
20 LC/MS $t = 3.66$ min, [MH^+] 415 consistent with the molecular formula $C_{19}H_{19}F_5N_4O$

- 25 Example 243: 2-(2-Fluoro-3-trifluoromethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide.

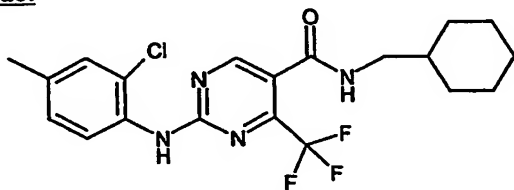


In a manner similar to Example 242, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (Example 166a) (50mg) in 1,4-dioxan (1ml) and 2-fluoro-3-trifluoromethylphenylamine (Aldrich) (156mg) were reacted to give the title compound (11mg)

- 30 NMR (Chloroform-d₆) δ 0.94-1.08 (2H, m), 1.15-1.34 (3H, m), 1.55- 1.59 (1H, m), 1.65-1.73 (1H, m), 1.73-1.83 (4H, m), 3.30 (2H, t), 5.91 (1H, bs), 7.28- 7.37 (2H, m), 7.74 (1H, bs), 8.65-8.73 (1H, m), 8.77-8.80 (1H, m)

LC/MS $t = 3.66\text{min}$ $[\text{MH}^+] = 465$ consistent with the molecular formula $\text{C}_{20}\text{H}_{19}\text{F}_7\text{N}_4\text{O}$

Example 244: 2-(2-Chloro-4-methylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide.



5

To a solution of 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (Example 166a) (50mg) in 1,4-dioxan (1ml) was added 2-chloro-4-methylphenylamine (Aldrich) (109mg) the mixture was stirred at reflux for 24 hours using a Radleys Greenhouse Parallel Synthesiser. The dioxan was removed using a nitrogen blow down unit. The residue was taken up into methanol (0.5ml) and dimethylsulfoxide (0.5ml) and purified using mass directed auto-preparative system to give the title compound) (24mg)

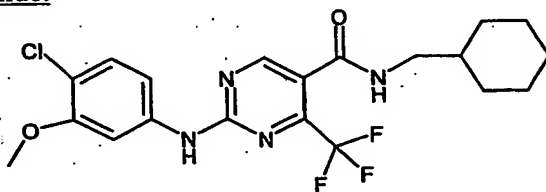
10

NMR (Methanol- d_6) δ 1.50-1.60 (2H, m), 1.70-1.89 (3H, m), 2.06-2.15 (1H, m), 2.2-2.26 (1H, m), 2.27-2.38 (4H, m), 2.88 (3H, s), 3.71 (2H, d), 7.68 (1H, d), 7.85 (1H, s), 8.31 (1H, d), 9.10 (1H, s).

15

LC/MS $t = 3.81\text{min}$, $[\text{MH}^+] = 427$ consistent with the molecular formula $\text{C}_{20}\text{H}_{22}^{35}\text{Cl F}_3\text{N}_4\text{O}$

Example 245: 2-(4-Chloro-3-methoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide.



20

In a manner similar to Example 243, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (Example 166a) (50mg) in 1,4-dioxan (1ml) and 4-chloro-3-methoxyphenylamine (Wychem) (122mg) were reacted to give the title compound (33mg)

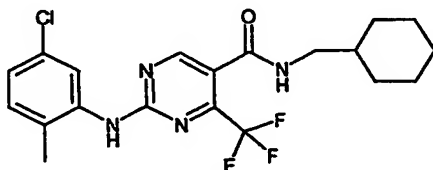
NMR (Methanol- d_6) δ 0.95-1.06 (2H, m), 1.20-1.34 (3H, m), 1.55-1.64 (1H, m), 1.65-1.71 (1H, m), 1.72-1.85 (4H, m), 3.19 (2H, d), 3.90 (3H, s), 7.18 (1H, dd), 7.27 (1H, d), 7.80 (1H, bs), 8.64 (1H, s).

25

LC/MS $t = 3.79\text{min}$, $[\text{MH}^+] = 443$ consistent with the molecular formula $\text{C}_{20}\text{H}_{22}^{35}\text{Cl F}_3\text{N}_4\text{O}_2$

Example 246: 2-(5-Chloro-2-methylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide.

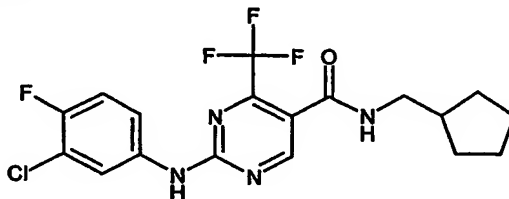
30



In a manner similar to Example 243, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (Example 166a) (50mg) in 1,4-dioxan (1ml) and 5-chloro-2-methyl aniline (Aldrich) (110mg) were reacted to give the title compound (36mg)

NMR (Methanol-d₆) δ 1.47-1.59 (2H, m), 1.72-1.89 (3H, m), 2.05-2.18 (1H, m), 2.19-2.25 (1H, m), 2.31 (4H, t), 2.79 (3H, s), 3.71 (2H, d), 7.76 (1H, dd), 7.76 (1H, d), 8.17 (1H, d), 9.09 (1H, s)
 LC/MS $t = 3.77$ min $[MH^+] = 427$ consistent with the molecular formula $C_{20}H_{22}^{35}ClF_3N_4O$

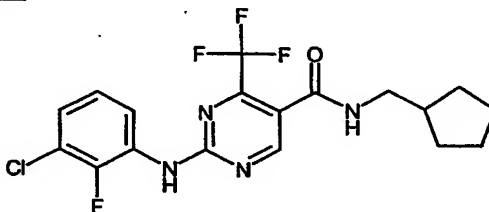
Example 247: 2-(3-Chloro-4-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide



2-Chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide (116mg Example 183a), 3-chloro-4-fluoroaniline (ex-Aldrich, 275mg), and 1,4-dioxan (1.2ml) were stirred at 100°C under nitrogen for 6h. The cooled reaction mixture was evaporated in vacuo, treated with ethyl acetate (5ml), washed with aqueous 2M hydrochloric acid (2 x 3ml), followed by brine, and dried (Na_2SO_4). The solution was evaporated in vacuo to give the title compound (104mg).

NMR δ (DMSO-d₆) 1.15-1.32 (2H, m), 1.46-1.66 (4H, m), 1.66-1.78 (2H, m), 2.1 (1H, q), 3.17 (2H, t), 7.4 (1H, t), 7.63-7.7 (1H, m), 8.05 (1H, dd), 8.61 (1H, t), 8.79 (1H, s), 10.6 (1H, s).
 LC/MS $t = 3.7$ min, Molecular ion observed $[MH^+] = 417$ consistent with the molecular formula $C_{18}H_{17}ClF_4N_4O$.

Example 248: 2-(3-Chloro-2-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide

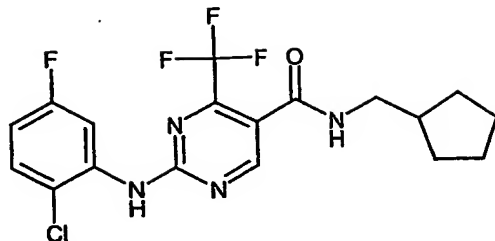


In a manner similar to Example 247, 3-chloro-2-fluoroaniline (ex-Aldrich, 275mg) was reacted for 18h, worked up analogously, then stirred in isohexane (6 ml), and filtered off to give the title compound (82mg).

NMR δ (CDCl₃) 1.2-1.34 (2H, m), 1.55-1.76 (>4H, m + H₂O), 1.78-1.89 (2H, m), 2.16 (1H, q), 3.41 (1H, t), 5.83-5.95 (1H, brt), 7.1-7.18 (2H, m), 7.28 (1H, s), 7.66 (1H, brs), 8.3-8.4 (1H, m), 8.75 (1H, s).

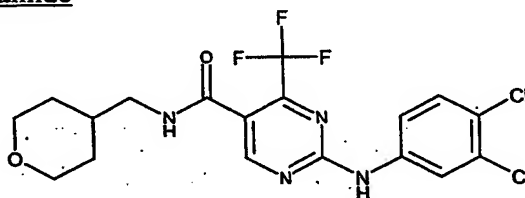
LC/MS $t = 3.7$ min, Molecular ion observed $[MH^+] = 417$ consistent with the molecular formula $C_{18}H_{17}ClF_4N_4O$.

Example 249: 2-(2-Chloro-5-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide



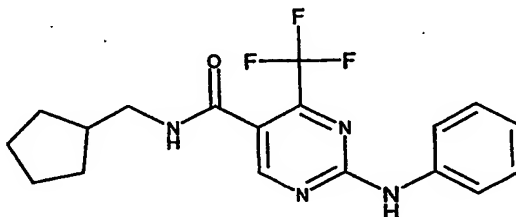
2-Chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide (100mg Example 183a), 2-chloro-5-fluoroaniline (ex-Fluorochem, 237mg), and 1,4-dioxan (1 ml) were stirred at 100°C under nitrogen for 18h. The cooled reaction mixture was evaporated in vacuo, treated with ethyl acetate (5 ml), washed with aqueous 2M hydrochloric acid (2 x 3ml), followed by water (2x3 ml), and dried (Na₂SO₄). The solution was evaporated in vacuo and the residue purified by mass directed autopreparative purification to give the title compound (35mg).
 NMR δ (CDCl₃) 1.2-1.35 (2H, m), 1.53-1.76 (>4H, m + H₂O), 1.78-1.90 (2H, m), 2.17 (1H, q), 3.41 (2H, dd), 5.9 (1H, brt), 7.0-7.11 (2H, m), 7.65-7.7 (1H, m) 8.56 (1H, dd), 8.79 (1H, s).
 LC/MS t = 3.67 min, Molecular ion observed [MH⁺] 417 consistent with the molecular formula C₁₈H₁₇ClF₄N₄O.

Example 250: 2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Reference Example 1(c) 2-(3,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30mg) and 4-aminomethyltetrahydropyran (20mg, ex CombiBlocks) afforded the title compound (38mg).
 NMR (DMSO-d₆) δ 1.18-1.25 (2H, m), 1.62 (2H, d), 1.74 (1H, m), 3.1 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.60 (1H, t), 7.69 (1H, m), 8.16 (1H, dd), 8.64 (1H, t), 8.84 (1H, s), 10.70 (1H, s)
 LC/MS, t = 3.45 min, Molecular ion observed (MH⁺) = 449 consistent with the molecular formula C₁₈H₁₇N₄O₂³⁵Cl₂F₃

Example 251: 2-(Phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethylamide



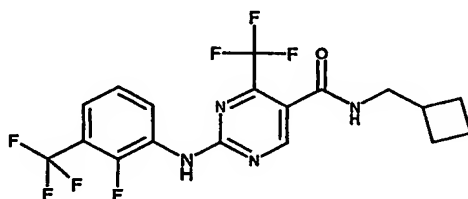
In a manner similar to Reference Example 1 (c), 2-(Phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30mg) and cyclopentylmethylamine hydrochloride (21mg) afforded the title compound (32mg) after purification by trituration with diethylether.

NMR (DMSO-d₆) δ 1.20-1.25 (2H, m), 1.48-1.72 (6H, m), 2.07 (1H, m), 3.13 (2H, t), 7.04 (1H, t), 7.34 (2H, t), 7.74 (2H, d), 8.58 (1H, t), 8.70 (1H, s), 10.35 (1H, s)

LC/MS, $t = 3.52$ min, Molecular ion observed (MH^+) = 365 consistent with the molecular formula $C_{18}H_{19}N_4O F_3$

5

Example 252: 2-(2-Fluoro-3-trifluoromethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



10

2-Chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclobutylmethyl-amide (200mg) in 2-fluoro-3-(trifluoromethyl)aniline (0.5ml) was heated at 180°C under microwave irradiation for 30 minutes. The residue was dissolved in dichloromethane and purified over silica gel (Merck 9385) using the Biotage Horizon system eluting with 10% ethylacetate / isohexane to 100% ethyl acetate gradient to afford the title compound.

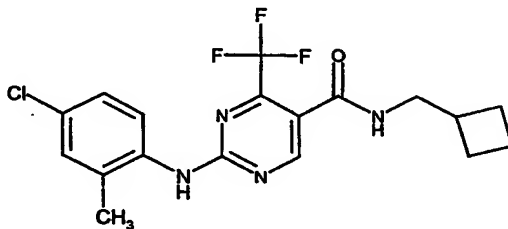
15

NMR (CDCl₃) δ 1.70-1.81 (2H, m), 1.86-2.00 (2H, m), 2.07-2.17 (2H, m), 2.51-2.65 (1H, m), 3.48 (2H, dd), 5.78-5.86 (1H, m), 7.25-7.36 (2H, m), 7.70-7.76 (1H, bs), 8.64-8.72 (1H, m), 8.75-8.79 (1H, s)

20

LC/MS, $t = 3.64$ min, Molecular ion observed (MH^+) = 437 consistent with the molecular formula $C_{18}H_{15}F_7N_4O$

Example 253: 2-(2-Methyl-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



25

To a solution of 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclobutylmethyl-amide (50mg) in 1,4-dioxan (1.0ml) was added 2-methyl-4-chloroaniline (120mg) and the solution heated at 180°C under microwave irradiation for 30 x 2 minutes. The residue was dissolved in 1:1 DMSO : methanol (1.0ml) and purified by Mass Directed Auto-Purification to afford the title compound (36mg).

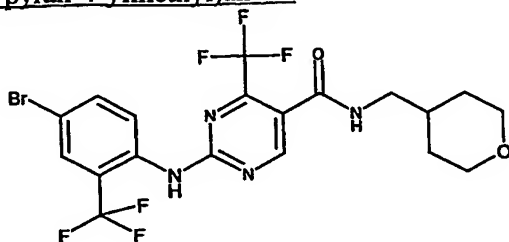
30

NMR (CDCl₃) δ 1.79-1.80 (2H, m), 1.85-1.99 (2H, m), 2.05-2.16 (2H, m), 2.25-2.63 (1H, m), 5.74-5.83 (1H, m), 7.15 (1H, bs), 7.2-7.78 (2H, m), 7.81 (1H, d), 8.66 (1H, s)

35

LC/MS, $t = 3.6$ min, Molecular ion observed (MH^+) = 398 consistent with the molecular formula $C_{18}H_{18}Cl F_3 N_4 O$

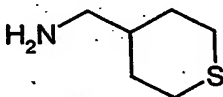
Example 254: 2-(2-trifluoromethyl-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl) amide



- 5 2-Chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (80mg) in 2- trifluoromethyl-4-bromoaniline (0.5ml) was heated at 190°C under microwave irradiation for 20 minutes. The sample was purified by mass directed auto-purification to afford the title compound (21mg).
- NMR (DMSO-d₆) δ 1.15-1.23 (2H, m), 1.57 (2H, d), 1.60 (1H, m), 3.09 (2H, t), 3.26 (2H, t), 3.84 (2H, d), 7.51 (1H, d), 7.95 (2H, m), 8.58 (2H, s,t), 10.00 (1H, s)
- 10 LC/MS, $t = 3.41$ min, Molecular ion observed (MH^+) = 529 consistent with the molecular formula C₁₉H₁₇N₄O₂F₆⁸¹Br

15 Example 255: 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydrothiopyran-4-ylmethyl) amide

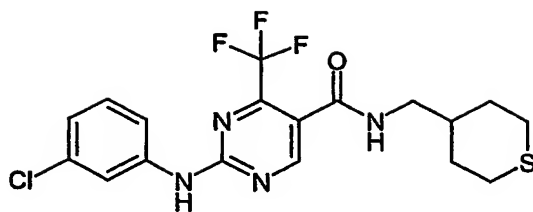
a) 4-(Aminomethyl)tetrahydrothiopyran



- 20 A solution of borane-tetrahydrofuran complex (1M in tetrahydrofuran, 11ml) was added over 5minutes to a solution of tetrahydro-2H-thiopyran-4-carbonitrile (1.27g) [Heimgartner et al, Helv. Chim. Acta 80(5), 1528 (1997)] in dry tetrahydrofuran (5ml) under nitrogen at room temperature. The solution was heated at reflux overnight, then cooled to 20°C. Methanol (15ml) was added dropwise keeping the temperature below 25°C, then the mixture was cooled to 0°C and dry
- 25 hydrogen chloride was bubbled through for 15mins. The resulting mixture was heated at reflux for 1.5 hours, evaporated and the residue re-evaporated twice from methanol. Ether (30ml) was added giving a white oily solid. The ether was decanted and the residue was dissolved in water (30ml) and extracted with dichloromethane (2 x 30ml). The remaining aqueous was made strongly basic with sodium hydroxide and extracted with dichloromethane (2 x 30ml). The
- 30 combined extracts were dried over potassium carbonate and evaporated to give the title compound (390mg)

NMR (DMSO) δ 1.2 (5H, m), 2.0 (2H, m), 2.36 (2H, m), 2.55 (4H, m).

- 35 b) 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydrothiopyran-4-ylmethyl) amide



In a manner similar to Reference Example 1b) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (95 mg) and 4-(aminomethyl)tetrahydrothiopyran (79mg) (above) gave the title compound (92mg).

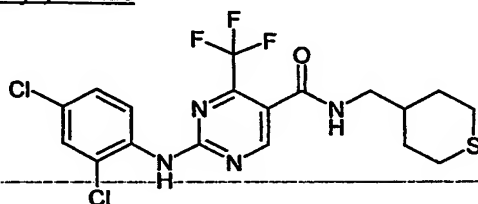
5

NMR (DMSO-d₆) δ 1.26 (2H, m), 1.55 (1H, m), 2.01 (2H, m), 2.60 (4H, m), 3.10 (2H, t), 7.09 (1H, m), 7.37 (1H, t), 7.65 (1H, m), 7.96 (1H, m), 8.63 (1H, t), 8.81 (1H, s), 10.6 (1H, s).

LC/MS CF111437, t_r = 3.61 min, Molecular ion observed (MH^+) = 431 consistent with the molecular formula $C_{18}H_{18}^{35}ClF_3N_4OS$

10

Example 256: 2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydrothiopyran-4-ylmethyl) amide



In a manner similar to Reference Example 1b) 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (106 mg) and 4-(aminomethyl)tetrahydrothiopyran (79mg) (Example 255a) gave the title compound (82mg).

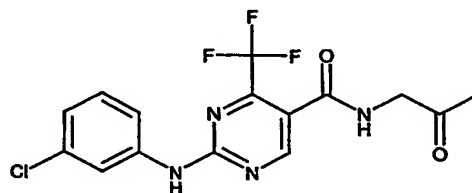
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NMR (DMSO-d₆) δ 1.27 (2H, m), 1.55 (1H, m), 2.00 (2H, m), 2.59 (4H, m), 3.08 (2H, t), 7.47 (1H, m), 7.57 (1H, d), 7.72 (1H, m), 8.59 (1H, t), 8.64 (1H, s), 10.0 (1H, s).

20

LC/MS CF111493, t_r = 3.70 min, Molecular ion observed (MH^+) = 465 consistent with the molecular formula $C_{18}H_{17}^{35}Cl_2F_3N_4OS$

Example 263: 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (2-oxo-propyl)-amide



25

To a stirred solution of 2-(3-chloro-phenylamino)-trifluoromethyl-pyrimidine-5-carboxylic acid (2-hydroxy-propyl)-amide (200mg) in dimethylsulfoxide (6.0ml) and triethylamine (324mg) at 0°C was added a solution of sulphur trioxide-pyridine complex (250mg) in dimethylsulfoxide (6.0ml). This was allowed to warm to room temperature and after 2 hours the mixture was diluted with dichloromethane and washed twice with 0.1N hydrochloric acid. The organic layer was dried

30

(Na₂SO₄) and evaporated. The sample was purified by mass directed auto-purification to afford the title compound (91mg).

NMR (DMSO-d₆) δ 2.15 (3H, s), 4.13 (2H, d), 7.10 (1H, d), 7.36 (1H, t), 7.67 (1H, d), 7.96 (1H, s), 8.84 (1H, s), 8.94 (1H, t), 10.55 (1H, s)

LC/MS, $t = 3.18$ min, Molecular ion observed (MH^+) = 373 consistent with the molecular formula C₁₅H₁₂N₄O₂F₃³⁵Cl

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Example 264: Inhalant Formulation

A compound of formula (I) or a pharmaceutically acceptable derivative thereof, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

Example 265: Tablet Formulation

<u>Tablets/Ingredients</u>	<u>Per Tablet</u>
1. Active ingredient (Compound of formula (I) or pharmaceutically acceptable derivative)	40 mg
2. Corn Starch	20 mg
3. Alginic acid	20 mg
4. Sodium Alginate	20 mg
5. Mg stearate	1.3 mg

Procedure for tablet formulation:

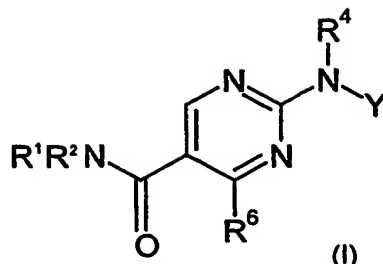
Ingredients 1, 2, 3 and 4 are blended in a suitable mixer/blender. Sufficient water is added portion-wise to the blend with careful mixing after each addition until the mass is of a consistency to permit its conversion to wet granules. The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen. The wet granules are then dried in an oven at 140°F (60°C) until dry. The dry granules are lubricated with ingredient No. 5, and the lubricated granules are compressed on a suitable tablet press.

Example 266: Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula (I) in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then rendered sterile by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

Claims

1. A compound of formula (I):



wherein:

Y is phenyl, optionally substituted with one, two or three substituents;

R¹ is selected from: hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or halosubstituted C₁₋₆ alkyl;

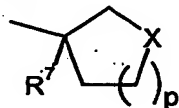
R² is (CH₂)_mR³ where m is 0 or 1;

or R¹ and R² together with N to which they are attached form an optionally substituted 4- to 8- membered non-aromatic heterocyclyl ring;

R³ is an optionally substituted 4- to 8- membered non-aromatic heterocyclyl group, an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted straight or branched C₁₋₁₀ alkyl, a C₅₋₇ cycloalkenyl or R⁵;

R⁴ is selected from: hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or halosubstituted C₁₋₆ alkyl, COCH₃, or SO₂Me;

R⁵ is



wherein p is 0, 1 or 2 and X is CH₂ or O;

R⁶ is methyl, chloro or CH_xF_n wherein n is 1, 2, or 3, x is 0, 1 or 2 and n and x add up to 3;

R⁷ is OH, C₁₋₆alkoxy, NR^{8a}R^{8b}, NHCOR⁹, NHSO₂R⁹, SOqR⁹;

R^{8a} is H or C₁₋₆alkyl;

R^{8b} is H or C₁₋₆alkyl;

R⁹ is C₁₋₆alkyl;

q is 0, 1 or 2;

and pharmaceutically acceptable derivatives thereof.

2. A compound as claimed in claim 1 wherein Y is a substituted phenyl.

3. A compound as claimed in claims 1 or wherein R⁴ is C₁₋₆alkyl or hydrogen.

4. A compound as claimed in anyone of claims 1 to 3 wherein R⁶ is CF₃.

5. A compound as claimed in claim 1 selected from any one of examples 1 to 263 or a pharmaceutically acceptable derivative thereof.

6. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 5 or a pharmaceutically acceptable derivative thereof and a pharmaceutical carrier or diluent thereof.

5

7. A method of treating a human or animal subject suffering from a condition which is mediated by the activity of cannabinoid 2 receptors which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) as claimed in anyone of claims 1 to 5 or a pharmaceutically acceptable derivative thereof.

10

8. A method of treatment as claimed in claim 7 wherein the condition is an immune disorder, an inflammatory disorder, pain, rheumatoid arthritis, multiple sclerosis, osteoarthritis or osteoporosis

Abstract

5 This relates to novel pyrimidine derivatives, pharmaceutical compositions containing these compounds and their use in the treatment of diseases, particularly pain, which diseases are caused directly or indirectly by an increase or decrease in activity of the cannabinoid receptor.

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